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Foreword

The concept of the Handbook of Hypertension developed in the late 1970s from a widespread feeling that the diversity of interests and inputs into hypertension research no longer lent themselves to publication in a single textbook. Moreover, it became apparent that some areas change and expand at a faster rate than others, thus necessitating different policies of revision and updating. Hence we preferred the option of a serial Handbook, with each volume covering separate topics.

The choice of topics in the series has resulted from lengthy discussions with many colleagues in clinical and basic science. Like the present volume on Blood Pressure Measurement, each volume is intended to be complete in its own right, and not dependent on other volumes in the series. We have accepted some degree of overlap between volumes, since this is unavoidable and, in our view, even desirable in such a broad field. In accordance with the basic concept sketched above, these volumes devoted to the most rapidly changing areas of interest have been or will be revised and updated. This policy is reflected in the titles currently in preparation:

Volume 15. Clinical Aspects of Hypertension – revised and updated version of Volumes 1 and 2 (Editor: J.I.S. Robertson)

The terminology used in the Handbook is oriented to the American style of spelling. Standardization has been adapted as far as possible to the recommendations issued by the World Health Organization. This applies to both units and drug names. The ‘Système International d’Unités’ (SI) as worked out by the intergovernmental ‘Conférence Générale des Poids et Mesures’ (CGPM) has been applied consistently, but with one notable exception: for blood pressure we have retained the millimeter of mercury (mmHg) in accordance with the recommendation of the International Society of Hypertension. This unit may not be consistent with the SI concept but has proved resistant to attempts at replacement over recent decades. In the same vein, the index of ‘International Nonproprietary Names (INN) for Pharmaceutical Substances’ has been followed as closely as possible, though with some exceptions. Starting from this volume the Vancouver style of referencing has been adopted.

This book, like the others in the series, reflects the views of the Volume Editors and individual authors. Our role has been limited to planning and overall coordination. It is a continuing privilege to collaborate with so many gifted and able colleagues in the preparation of the Handbook of Hypertension.
We and the Publishers believe that the series will continue to develop to meet the needs of the growing circle of those involved with hypertension, as both a disorder and a phenomenon.

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Introduction

As quantification is the key to clinical investigation and practice, it was deemed appropriate to have a volume on blood pressure measurement in the *Handbook of Hypertension* series. Blood pressure measurement is bedevilled by problems related to blood pressure variability — virtually a moving target, and here ambulatory blood pressure measurement may overcome the problems associated with isolated blood pressure values not being representative of blood pressure behavior over time. The growing importance of ambulatory blood pressure measurement is reflected in our having four chapters dealing with various aspects of this topic and it is touched upon in other chapters.

Accuracy, or rather the lack of accuracy of blood pressure-measuring devices, is another cause for concern. It is rather disturbing that many of the devices used in the landmark hypertension studies were probably not accurate to the degree that one might expect the measurement of any key variable in clinical research. There are also important clinical subgroups that would require special consideration, for example the elderly, children, pregnancy, patients undergoing anesthesia as well as blood pressure measurement in laboratory animals, that have been addressed in separate chapters.

Our contributors have also taken a look back (Chapter 1) at the history of blood pressure measurement, and also attempted to foresee the future (Chapter 20).

Two interesting issues have recurred during the writing and editing of this volume. The first of these is to do with the spelling of Korotkoff's/Korotkov's name. We have on the advice sought decided to use the latter as being the most appropriate. The second and more problematic issue is the use of SI units for quantification. While the general concept of SI units has been embraced enthusiastically in Europe, less so in the United States, most workers in hypertension, be they clinicians or investigators, have quite rightly drawn the line at the proposed introduction of the kilopascal to hypertension on the basis that the physical measurement is carried out, in the majority of cases using the height of a mercury column, and to translate this to SI units for conformity with the general move to such units is unwarranted and unhelpful.

Because many of the documents setting down recommendations on blood pressure measurement and standards in relation to validation and instrumentation are dispersed in sources not always readily available, it was considered appropriate to reproduce the most important of these in the form of appendices so as to facilitate ready access.

There is a substantial amount of research into various aspects of blood pressure measurement currently under way in the areas of standards, instrumentation, ambulatory blood pressure measurement, and most importantly in applying these techniques to characterize blood pressure behavior in more detail, with a long-term goal of optimizing patient management. We have written elsewhere — 'there can be
little doubt that the measurement of blood pressure whether by conventional sphygmomanometry with expensive and elaborate automated devices, non-invasively with ambulatory devices by patients in their homes, or by direct intra-arterial techniques is fraught with numerous potential errors. Yet, in clinical research we have been making important decisions both in relation to patient management and scientific research, with a disregard for the limitations of the techniques available. We hope that the present volume will raise awareness about these limitations, and, in addition, alert readers to the opportunities for clinical practice and research offered by accurate blood pressure measurement.

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1. The history of indirect blood pressure measurement

Eoin O’Brien and Desmond Fitzgerald

That the phenomenon of blood spurting from a severed artery failed to excite the minds of scientists until relatively recently may be seen as an indictment of the development of scientific reasoning (Fig. 1). That the discovery of blood pressure was virtually ignored by the scientific community for almost a century is somewhat more remarkable. This essay which opens, therefore, on a critical note will be seen to end on one of scepticism — scepticism at the tardiness of scientific thinking, even today, to grasp the obvious and thereby advance science. Such are the lessons that may be learned from the study of history.

This chapter will consider the subject under the following headings which outline only in the broadest sense the development of thought in blood pressure measurement:

I. Direct Measurement of Systolic Blood Pressure ca. 1733
II. Indirect Measurement of Systolic Blood Pressure ca. 1855
III. Measurement of Systolic and Diastolic Blood Pressure by Oscillometry ca. 1900
IV. Auscultatory Measurement of Systolic and Diastolic Blood Pressure ca. 1905
V. Development of Automated Techniques ca. 1940
VI. Ambulatory Measurement of Blood Pressure ca. 1960

The development of blood pressure measurement should not be viewed as a clear progression from one principle or device to the next; many of the instruments described in this review often developed simultaneously and, at times, independently in different centers. Moreover, the introduction of a superior technique did not necessarily result in the demise of its predecessor for many years, but it is helpful to impose a scheme which permits us to assess the progression of scientific ideas in blood pressure measurement.

I. DIRECT MEASUREMENT OF SYSTOLIC BLOOD PRESSURE

The ancient Egyptians, as the Ebers papyrus of 1500 B.C. show, were undoubtedly aware of the pulsations in different parts of the body even if they did not actually go as far as to count the pulse (1). Egyptian physicians, moreover, regarded

measurement an an indispensable aspect of clinical assessment, but the measure-
ment of blood pressure had necessarily to await the discovery of the circulation by
William Harvey (1578–1657) in 1628 (2). In fact, over a century had to pass before
the Reverend Stephen Hales (1677–1761) performed his famous experiment in 1733
demonstrating that blood rose to a height of 8 feet, 3 inches in a glass tube placed
in the artery of a horse (Fig. 2). He went on to show that exsanguination reduced
this pressure and he also did a number of intriguing experiments on the velocity of
Fig. 2. The Reverend Hales demonstrating blood pressure in a horse. Reproduced from: *History of hypertension series*. Sandwich, Kent: Pfizer Ltd., 1980.
blood flow (3). Hales, a divine and humanitarian, had a profound influence on social mores (4, 5) and scientific thought but, once again, his remarkable discovery of blood pressure was to lie fallow for nearly a hundred years. The failure of physiologists to apply Hales's discovery to human physiology is, perhaps, not surprising as the insertion of glass tubes measuring seven and a half feet — such was Hales's overestimation of human blood pressure (5) — was not likely to meet with general acceptance. A more acceptable measuring device was needed. This was provided by Jean-Léonard Marie Poiseuille (1799–1869) who reported the measurement of blood pressure with a mercury sphygmomanometer in 1828 (6), thereby

winning a gold medal from the Royal Academy of Medicine in Paris (7). Poiseuille recorded blood pressure in a variety of arteries in animals by connecting his U-shaped mercury manometer to the artery with leaden cannulas. He prevented the coagulation of blood by filling the tube leading from the artery with potassium carbonate. Poiseuille’s device, or modifications of it, were widely used to study the effect of physiological maneuvers and drugs on systolic blood pressure (8). In fact, as Lawrence has pointed out, the technique of direct measurement of arterial blood pressure in animals had become quite sophisticated in the second half of the nineteenth century (9).

In 1847, Carl Ludwig (1816 – 1895), Professor of Comparative Anatomy at Marburg, made an even more significant advance than Poiseuille when he floated a writing pen on the mercury column of Poiseuille’s manometer and, using a revolving smoked drum, introduced the kymograph (10) which was to find wide application in physiological studies (11) (Fig. 3). This instrument was used by Faivre during a limb amputation to record systolic blood pressure for the first time in man (12). So dawned the next phase in the history of blood pressure measurement — the development of methods for indirectly measuring blood pressure in man.

II. INDIRECT MEASUREMETN OF SYSTOLIC BLOOD PRESSURE

The first device for measuring blood pressure indirectly is usually attributed to Karl Vierordt (1818 – 1864) who invented the first of many sphygmographs in 1855 (13) (Fig. 4). However, credit for the first instrument capable of measuring blood pressure indirectly should go to Jules Herisson, who, in 1833, devised an instrument which consisted of a mercury reservoir covered by a rubber membrane from which a graduated glass column arose (Fig. 5). The mercury bulb was compressed against the radial artery until oscillations ceased in the mercury column at which point systolic pressure was estimated. Herrison described an association between a full

pulse, left ventricular hypertrophy and apoplexy but inexplicably gives no blood pressure measurements in such patients (14). Vierordt and Herrison's instruments were each to influence the development of many blood pressure measuring devices in the nineteenth century.

**Instruments based on the Vierordt sphygmograph**

Vierordt's sphygmograph was a large (168 cm long) instrument consisting of a levered system that recorded the movements of a weight resting on the radial artery.
This provided pulse wave recordings similar to intra-arterial recordings and an estimate of blood pressure was obtained by determining the weight required to obliterate the pulse (11). Understandably, this instrument was inaccurate.

The talented and versatile French physiologist, Etienne Jules Marey (1830 – 1904) (Fig. 6), quickly recognized the potential of Vierordt’s instrument which he simplified and made more accurate (15). A number of modifications of this device became available, a good collection of which is to be found at the Wellcome Museum (16). In Marey’s sphygmograph, the lever system and weights of Vierordt’s device were replaced by a metal spring, the tip of which overlay the artery (Fig. 7). An adjustable screw altered the pressure exerted by the spring and a recording system wrote on smoked paper driven by a clockwork mechanism. The device, which was light, was strapped to the wrist with a laced bandage. Recordings were remarkably similar to direct intra-arterial tracings with the diazotic notch being clearly visible. Marey was more interested in the pulse wave form than the actual blood pressure and his original device could only give an inaccurate estimate of blood pressure. Balthazar...
Foster modified the instrument in an attempt to overcome its inaccuracy deficiency by calibrating the pressure screw to provide an estimate of the pressure required to obtain a maximal pulse tracing (17). A number of other modifications were made to Marey's sphygmograph (16), the most elaborate being those of the young physician from Guy's Hospital, Frederick Mahomed (1849–1884) (18) (Fig. 8). He was the first to make a serious study of the association of raised blood pressure with other illnesses, most notably Bright's disease (19). At the same time Thomas Lauder Brunton was using the Marey sphygmograph to study the effects of drugs on blood pressure (20). Important though the Marey sphygmograph was as a landmark in sphygmomanometry, it was difficult to use, likely to give varying results between observers, and it was inaccurate because it measured total pressure applied to the artery rather than pressure per unit of surface, as Theodore Janeway pointed out.

*Fig. 7. Sphygmograph of Marey. Reproduced from: Snellen HA. E.J. Marey and cardiology. Rotterdam: Kooyker Scientific Publications, 1980; 214.*

*Fig. 8. Mahomed sphygmograph. Old illustration (source unknown).*
in his comprehensive review of the history of blood pressure measurement written in 1904 (21). Not surprisingly, therefore, its use was confined to the laboratory and it did not achieve clinical popularity.

The Marey sphygmograph was finally replaced by a simpler and more accurate device introduced by Robert Ellis Dudgeon (1820 – 1904), a homeopath, in 1882 (22) (Fig. 9). This lightweight device which could be carried in the pocket (it weighed 4 ounces and measured 2’’ x 2½’’) incorporated many of the principles of the Marey instrument, but it was less complicated. Pressure was applied to the radial artery using a calibrated screw and a clockwork motor drove a strip of smoked paper under an oscillating metal tip to provide a record of the pulse wave. This device, which proved extremely popular, was modified by Mortimer Granville (1833 – 1900) so that it could be folded to lie flat when not in use (23) and in 1885 Benjamin Ward Richardson improved the recording facility (24). The Dudgeon sphygmograph or one of its modifications soon became an essential piece of equipment for the physiologist or scientifically minded clinician. Many of the observations of Thomas Lewis, F.A. Mahomed, Sir James Mackenzie and Lauder Brunton are based on these devices (23).

However, the sphygmograph, in general, was a disappointment (9). It was capable of giving a pulse wave tracing but was not an accurate device for measuring blood pressure, if for no other reason than it failed to take into account the size of the arterial surface being compressed (9). Clifford Albott recognizing the problems of sphygmography advocated that physicians should be ‘... driven back upon the first, the readiest and still least dispensable of pulse gauges, namely the finger’ (25).
Instruments based on palpatory occlusion

As far back as 1833 Herrison had attempted to measure blood pressure by applying pressure directly to the radial artery (14) and now some 35 years later this principle was to be adopted again. These devices, of which there were many varieties (9), contained a springed mechanism which registered the pressure that had to be exerted either on a finger palpating the radial artery or directly on the artery to cause arterial occlusion. The spring of the device either moved a pointer along a scale as in the Batten sphygmomanometer (26) or pushed a calibrated cylinder out of the top of the instrument as in the Bloch sphygmomanometer (27). These instruments were difficult to use as the palpating finger, which had the important role of denoting obliteration of the pulse, had to remain totally passive and this was not easily achieved. Moreover, they were flawed in the same way as the sphygmographs of Marey and Dudgeon in that they applied pressure directly to the artery. Though these devices remained popular well into the twentieth century, they were soon to be replaced by the next generation of blood-pressure-measuring devices which depended on arterial occlusion by counter-pressure applied directly to the artery through a fluid medium rather than by direct pressure. Blood pressure was determined by palpation of the artery distal to the point of occlusion or by attached manometers. These devices were to become the direct forerunners of the modern sphygmomanometer.

Arterial occluding devices

It is now necessary to go back some years to determine how this new approach to blood pressure measurement evolved. In 1875, von Kries, who worked in Ludwig's laboratory attempted to estimate the absolute pressure in skin capillaries by measuring the weight needed to blanch the skin (28). Around the same time Marey, using air to compress an arm in a glass box, demonstrated the blanching of the arm occurred when systolic pressure was exceeded (29). Later Marey substituted water for air as the compressing medium and he recorded oscillations in plethysmographic pressure using a tambour writing system (9). These methods are, of course, inaccurate because the precise pressure level in the plethysmograph at which arterial pulsation disappears is difficult to determine. However, these techniques led Samuel Siegfried Ritter von Basch (1837 – 1905) to develop what he called the 'sphygmomanometer' in 1880 (30) (Fig. 10), which was the first reasonably accurate device for clinical measurement of blood pressure.

Using an experimental system of rubber tubes connected to cadaver arteries he showed that the pressure required to occlude the lumen of an artery was equal to the pressure within the vessel plus that required to overcome the rigidity of its wall. As the rigidity of arteries was small, the occlusion pressure was a good estimate of intra-arterial pressure. In von Basch's original instrument, the compressing medium, water, was enclosed in a rubber 'pelotte', or bulb, which had a thin membrane on one side. Pressure was applied on the radial (or temporal) artery with the pelotte and as the pressure increased water was forced out of the pelotte into the closed arm of the manometer; the pulse was palpated with the fingers of the other hand, just beyond the point of compression, and the point of disappearance was taken as
systolic pressure. Von Basch's instrument differed from those that had gone before in the important principle of providing pressure per unit of surface. Initially, the disappearance of the pulse was most easily determined by palpation, but later von Basch connected the device to a sphygmograph to register the obliteration of the pulse. The instrument went through many modifications, the most significant of which was made by von Basch himself who substituted the mercury manometer with an aneroid manometer, designed by Lucien Vidie (1805 – 1866) (9) and it was eventually refined to portable dimensions making it suitable for clinical use (Fig. 11). Extensive physiological and clinical observations were made with von Basch's

sphygmomanometer by Ignaz Zadek, who in 1880, was probably the first to observe the variability of blood pressure under different circumstances (31).

Pierre Carl Edouard Potain (1825 – 1907), Professor of Clinical Medicine at the Charité in Paris, made a further significant modification to von Basch’s instrument by substituting air for water as the compressing medium in the pelotte (Fig. 12). The pressure of air in the pelotte was raised to 30 mmHg through a side arm of the manometer tube and the zero position of the manometer was adjusted. Initially Potain used a U-tubed mercury manometer attached to the waistcoat button-hole of his junior doctor but later replaced this with an aneroid manometer.

In 1898 Leonard Hill (1866 – 1952) and Harold Barnard (1868 – 1908) published a modification of the von Basch/Potain sphygmomanometer in which pressure was recorded in a tube arising vertically from a modified pelotte, thus making the device easily portable (33). In 1898, George Oliver, produced a ‘haemodynamometer’ in which the movements of a pelotte membrane were amplified by a needle which moved a pointer across a scale (34).

These devices which owe their origin to von Basch, whom Janeway credits as ‘the inventor of clinical sphygmomanometry’, were flawed in that it was assumed that the artery could be uniformly compressed against underlying bone — a serious source of error (35).

The fin de siècle stage was dominated by the Austrians and French who had contributed substantially to the developing speciality, not least through Marey, whose contribution is detailed in an interesting book published in 1886 by Ozanam who himself made a number of modifications to existing sphygmomanometers (36). The Italians, however, would soon take the limelight.

![Marey Finger Device](image)

Limb-occluding devices

In some of his early experiments on blood pressure measurement Marey had used a water-filled plethysmograph to apply pressure to the entire arm (29) and he later modified this apparatus for the finger instead of the arm (37) (Fig. 13). However, the oscillations recorded were small and to overcome this problem, Mosso, in 1885, applied pressure to four fingers of each hand inserted into rubber stalls within metal tubes (38) (Fig. 14). This apparatus, though cumbersome, was quite accurate.

The next step to an occluding arm cuff was made by Scipione Riva-Rocci (1863 – 1939) in 1896 (39) (Fig. 15). Riva-Rocci’s cuff consisted of an inflatable rubber bladder enclosed in still leather encircling the upper arm. The bladder was in-
flated by a pump until the palpated pulse disappeared and the pressure was recorded by a mercury manometer (Fig. 16).

A year after Riva-Rocci’s publication Hill and Barnard described an almost identical instrument except that an aneroid gauge was used instead of a mercury manometer (40) (Fig. 17). Shortly afterwards Gaertner applied the same principle, namely, that of circular compression of an extremity, to the finger with an instrument which he called a ‘tonometer’ (41, 42) (Fig. 18). These techniques removed the


most serious error of their predecessors, namely that associated with achieving uniform compression of the radial artery against bone with the small and awkward pelotte. However, it was not long before a serious source of error was identified in the new devices. Heinrich von Recklinghausen (not to be confused with Friedrich von Recklinghausen of eponymic renown) in a series of elegant experiments in 1901, showed that the 5-cm-wide cuff used by Riva-Rocci gave erroneously high systolic pressures which could be corrected by using a 12-cm-wide cuff (43) and this was later confirmed by Janeway (44) and Erlanger (45).

The stage was now set for the next major development in blood pressure measurement, namely the measurement of both systolic and diastolic pressure. Though the instruments of Mosso (38) and Hill and Barnard could be used to estimate diastolic pressure by observing the point of maximum oscillation, mean and diastolic
pressures were often confused with each other and the significance of the latter was not clearly recognized at the close of the nineteenth century (46).

III. MEASUREMENT OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE BY OSCILLOMETRY

It is salutary to note that a century ago Theodore Caldwell Janeway (1872 – 1917), Visiting Physician to the City Hospital in New York, was as fully aware of the sources of error in the blood pressure measuring technique to which we so frequently draw attention today, namely the importance of ensuring that the arm is both relaxed and at heart level during measurement, that the cuff is deflated slowly, that an interval is allowed between measurements, and that ‘an armllet of 12 cm width is adequate for any but the most enormous arms’ (47). Janeway also anticipated the expansion that was about to take place in clinical sphygmomanometry and he recognized that this development would bring its own problems: ‘The gradual development of various sphygmomanometers from which one may chose a clinical instrument to-day (1904), has been unfortunate in breeding more partisan bias and personal feeling than should find a place in the quest of scientific accuracy; but this evil has not been without its good side. It has led to the rigid scrutiny of each new instrument brought forward, and a diligent search for its faults’ (48).

As is often inevitable in the research of medical history, the issue of priority for a particular discovery arises and in blood pressure measurement we find a number of such conundrums. The first of consequence is whether Riva-Rocci (39) or Hill and Barnard (40) should be accredited with inventing the forerunner to the modern sphygmomanometer. Janeway took the view that, though Riva-Rocci published first, ‘it is questionable whether the credit of the new device does not belong to Hill’ (49). This view can hardly be sustained, but perhaps by allowing the credit for this discovery to rest with the Italians, we can attribute, without fear of contention, a discovery of possibly greater importance to the London scientists, namely the development of a device capable of recording both systolic and diastolic blood pressure (40). It is of interest to note, however, that though Hill and Barnard mention diastolic blood pressure in their original publication (40), they confuse mean pressure for diastolic pressure and it was left to other workers, such as Janeway (50), to describe the correct use of the device by demonstrating that the point of maximum oscillation of the needle corresponded to diastolic and not to mean pressure.

The main disadvantage of Hill and Barnard’s sphygmomanometer was that the gauge became inaccurate with use and frequent recalibration was necessary, an occurrence which led Janeway to draw attention to a difficulty with which we are all too familiar with to-day: ‘The manometer is also difficult of repair in this country, a considerable drawback to so costly an apparatus (U.S. $40)’ (51). To overcome this weakness, attention was directed to determining diastolic blood pressure by observing the oscillations in a mercury manometer rather than on an aneroid gauge and Janeway produced a sphygmomanometer incorporating for the first time most of the features that are found in contemporary sphygmomanometers (52). The Janeway instrument had an extendible U-tube mercury manometer, it was portable,
the armlet contained an inflatable bladder measuring $12 \times 18$ cm, and it was reasonably priced at U.S. $14$ (Fig. 19).

In the early years of the twentieth century the most accurate research device for measuring systolic and diastolic blood pressure was an instrument invented by a physiologist at Johns Hopkins Hospital and future Nobel prizewinner, Joseph Erlanger, which incorporated all the recent developments, but in addition oscillations within the cuff were recorded across a membrane by means of an ingenious stop-cock and observer bias was removed by using a kymograph to record the oscillations of the mercury column (45, 53) (Fig. 20). It was, of course, too bulky for clinical use. In England, Gibson modified Erlanger’s device by using circular compression to estimate the systolic pressure and the oscillations of mercury to measure diastolic pressure (54) and Singer produced a further modification in 1910 (55) (Fig. 21).
In 1906, von Recklinghausen published details on diastolic blood pressure measurement using an aneroid tonometer (56) and three years later Dr. V. Pachon, Chef du Laboratoire de Physiologie in the Faculty of Medicine of Paris, successfully incorporated Erlanger's membrane in a portable recorder with an aneroid gauge (57). Known initially as a 'sphygmo-oscilometer' and later simply as an 'oscilometer' (Fig. 22), this instrument enjoyed popularity for many years and is prominently listed in catalogues of the thirties (Price £5 5s.0d.) (58).

Fig. 21. Gibson’s recording sphygmomanometer. Reproduced from: Halls Dally JF. *High blood pressure: its variations and control, 2nd ed.* London: W Heinemann, 1926; 248.

Such devices brought sphygmomanometry into clinical medicine and so dawned a new era but not without protest. One commentator, while acknowledging that ‘the middle-aged and successful physician may slowly and imperceptibly lose the exquisite sensitiveness of his finger tips through repeated attacks of gouty neuritis’, doubted if the sphygmomanometer would be welcomed by ‘the overworked and underpaid general practitioner, already loaded with thermometer, stethoscope, etc.,
etc., . . . ’ (59). Harvey Cushing was probably the first to advocate the charting of blood pressure on the bedside chart together with the temperature and pulse rate (60).

IV. AUSCULTATORY MEASUREMENT OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

In April 1905, a Russian surgeon, Nicolai Sergeivich Korotkov, presented a brief paper to the Imperial Military Academy in St. Petersburg which founded the technique of auscultatory measurement of systolic and diastolic blood pressure (61) (Fig. 23):

The cuff of the Riva-Rocci is placed on the middle third of the upper arm; the pressure within the cuff is quickly raised up to complete cessation of circulation below the cuff. Then, letting the mercury of the manometer fall one listens to the artery just below the cuff with a children’s stethoscope. At first no sounds are heard. With the falling of the mercury in the manometer down to a certain height, the first short tones appear; their appearance indicates the passage of part of the pulse wave under the cuff. It follows that the manometric figure at which the first tone appears corresponds to the maximal pressure. With the further fall of the mercury in the manometer one hears the systolic compression murmurs, which pass again into tones (second). Finally, all sounds disappear. The time of cessation of sounds indicates the free passage of the pulsewave; in other words, at the moment of the disappearance of the sounds the minimal blood pressure within the artery
predominates over the pressure in the cuff. It follows that the manometric figures at this time correspond to the minimal pressure. (62)

William Dock has commented that 'the most remarkable fact about the Korotkoff sound is that it was discovered' (63). What is even more remarkable is that the sounds had been discovered some years before Korotkov published his masterly paper. In 1901, Theodore Janeway, published a 20-page review of blood pressure measurement in the New York University Bulletin of the Medical Sciences in which he wrote: '... that certain experiments in a number of cases concerning the pressure tone and murmur in the brachial, to be described later, show that the pro-

duction of the tone always occurs at a lower pressure than the point in question (disappearance of secondary waves)' (64). He concluded the paper with another tantalizing statement that undoubtedly indicates that he was well on the way to making a notable discovery: 'It is to be hoped that some more satisfactory method for estimating mean arterial pressure may yet be devised. I have been making some experiments on the tone and murmur produced in the brachial artery by known pressures, thinking that some information might thus be obtained. The results will be reported in a subsequent article together with a consideration of the value of our present methods from a clinical standpoint'. Unfortunately Janeway did not elaborate on this intriguing statement and he makes no mention of auscultatory phenomena in his extensive monograph written in 1904. Had he done so, we might now speak of 'Janeway sounds' but such is Korotkov's succinct description that eponymous approbation cannot be challenged.

Indeed, Korotkov's discovery might have languished in obscurity were it not for two of his contemporaries, D.O. Krilov and M.V. Yanovski. Within a year of Korotkov's presentation, Krilov published a paper entitled 'On measuring the blood pressure with the sound method of Korotkov' in which he described elaborate experiments attempting to elucidate the mechanism of Korotkov sound production (65). Yanovski verified the accuracy of the technique and the technique was known for some time as the Korotkov-Yanovski Method (66). Ettinger is credited with describing the 5 phases of Korotkov sounds audible on cuff deflation (67). The 'silent gap' was described in the English literature by Cook and Taussag (68) in 1917 and according to Geddes and colleagues this did not inspire confidence in the technique (69). Gibson (70) attributed the first description of this phenomenon to a Frenchman, Tixier, who considered it to be a manifestation of mitral stenosis.

The Korotkov technique apparently became popular in Germany immediately, but there was a delay of some years before it reached the American and British literature. The technique was first introduced to British practice by George Oliver (without acknowledgement to Korotkov) in 1910 at a meeting of the Royal Society of Medicine which was reported briefly in The Lancet (71). The first detailed account of the new method (again without acknowledgement to Korotkov) was by Lauder Brunton later in 1910 (72). The technique was not accepted readily, and in the year following these first descriptions Gibson expressed the view that 'the auscultatory determination cannot replace the previous tactile determination' (73). In America a comprehensive description of the method was published in the Archives of Internal Medicine by J.C. Gittings in 1910 (74). In this paper he acknowledged the growing controversy as to whether muffling or disappearance of sounds should be taken as diastolic pressure but supported Korotkov and Ettinger in recommending the fifth phase. Such was to be the American view in the early years of the controversy, but in Germany and Britain the muffling of sounds rather than their disappearance was advocated (75). Measurement of diastolic blood pressure at the point of disappearance, as originally recommended by Korotkov, fell out of fashion within a few years and in 1926 we find Halls Dally quoting many studies demonstrating the superiority of muffling of sounds rather than disappearance as the most accurate measure of diastolic pressure (76), a view which he endorsed in the third edition of his influential book in 1934 (77). This view was to persist until comparatively recently when Korotkov's original recommendation was once again
adopted (78). A more recent controversy has focused on the need to measure diastolic blood pressure at all. Systolic blood pressure, which is easier to measure accurately in clinical practice and does not require as complicated technology for automated measurement, may provide the same epidemiological information as measuring both pressures (79–81). This issue remains to be resolved.

The source of the Korotkov sounds has been debated since they were first described. Korotkov, defending his technique, was of the opinion that the sounds were of local origin and not transmitted from the heart (61). Krilov studied the sounds in a number of experiments and concluded that they were produced by the fluctuating or centrifugal movement of the blood particles and the simultaneous vibration of the vessel wall (65). Ettinger, to whom may be attributed the clear delineation of the 5 phases of the Korotkov sounds in 1907, summarized the early and very important literature on the Korotkov technique and supported Korotkov in his opinion that the sounds were of local rather than transmitted origin (67). In this eloquent scientific paper he attempted to define the clinical significance of Phases II and III, and in 1911, Goodman and Howell also described the alterations in these phases that might occur in disease, in terms of both force and duration (82). Interestingly, contemporary clinical investigators in hypertension have been content to ignore the

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significance of these forgotten phases of the Korotkov sound phenomenon. Both flow phenomena and the transmission of sonic vibrations from the artery are now considered to contribute to the production of the sounds (83, 84), but their precise origin is complex and difficult to elucidate (70). The subject has been reviewed comprehensively by Geddes (85).

It is of interest to reflect that in 1918 the technique was treated as an important clinical procedure requiring considerable care and attention if accurate results were to be obtained. Among recommendations relating to patient anxiety, posture, arm level and an unequivocal direction to measure diastolic pressure at the disappearance of sounds there is also a recommendation to withhold diagnostic decisions until a number of measurements have been made under varying conditions. In recording the results of measurement, the observer is asked to make note not only of the blood pressure, but also of the apparatus used, the width of the cuff, the limb examined and whether right or left and the time of day as well as the date (86). We might well ponder how these aspects of the technique of blood pressure measurement were obscured in the mists of time.

Fig. 25. Multiple sphygmonometerscope. Reproduced from: Faught FA. Blood-pressure primer. The sphygmonanometer and its practical application. Philadelphia: GP Pilling, 1918; 42.

The age of clinical sphygmomanometry now began in earnest and with it came a problem which is all too familiar to-day: 'At the present time (1918) the market is flooded with instruments of all descriptions for estimating blood-pressure, so that it is important that the prospective purchaser should be able to separate the good from the bad . . . ' (87). There were mercury instruments with manometers incorporating a mercury reservoir and others with a U-tube similar to that first described by Poiseuille; there were a variety of aneroid devices which were marketed as 'pocket sphygmomanometers' (Fig. 24); in addition, there were specially designed stethoscopes for measuring blood pressure and a 'Multiple Sphygmometroscope' for training observers was also available (86) (Fig. 25).

By 1926 modern sphygmomanometry had been well established and a large variety of U-tube mercury and aneroid sphygmomanometers were available (88). Simple U-tube mercury manometers, such as that designed by Professor C.J. Martin (Fig. 26), were popular (89), but an important modification was introduced in the 'Baumanometer' which utilized for the first time a modified U-tube and mercury
reservoir (Fig. 27). The manufacturers marketed the instrument with the claim that every instrument was individually calibrated against a standard mercurial manometer, the accuracy of which had been checked against the U.S. Bureau of Standards manometer in Washington. Halls Dally, being of the opinion that such a claim was so important 'that it needs substantiation', submitted the Baumanometer to the National Physics Laboratory at Teddington, which confirmed the manufacturer's claim (90). Would that we exercised such cautious scepticism to-day!

In 1928, Pachon's sphygmo-oscillometer was still in use and was combined with auscultation to provide both auscultatory and oscillometric readings. Indeed Boullitte devised an aneroid sphygmomanometer which, by using a stethoscope attached
to an armband, could be used to measure blood pressure by the Korotkov auscultatory, the oscillometric technique and the old palpatory method (91).

In the 1934 edition of Halls Dally’s book a variety of aneroid devices were featured — the improved Brunton sphygmomanometer, the Boulette sphygmomanometer, the Tycos aneroid sphygmomanometer and a particularly robust device, the arteriotensiometer of Donzelot (92) (Fig. 28). Some of these devices utilized Gallavardin’s armlet containing two rubber bladders overlapping by about one third of their widths to give an overall width of 12 cm, which it was claimed gave more uniform compression of the artery than a single bladder. It was recommended that aneroid devices should be tested against a standard mercury manometer every 2 years because of loss of accuracy.

A number of interesting devices for obtaining graphic recordings of blood pressure are described by Halls Dally (93). The Tonoscillograph of Plesch consisted of two manometers and a rotating drum with a graduated paper disk on which the blood pressure was recorded by a writing pen. Boulitte’s Portable Recording Oscillometer (Fig. 29) utilized a clockwork recording system and aneroid manometer. The Tycos Recording Sphygmo tonograph (Fig. 30), an elaborate disc recording device, is an indication of the importance that was being attached to blood pressure measurement at this time. In research, equipment was being adapted for the direct recording of intra-arterial blood pressure, as with the Boullittograph (94) (Fig. 31).
Fig. 29. Boulite’s portable recording oscillometer. Reproduced from: Halls Dally JF. High blood pressure: its variations and control, 2nd ed. London: W Heinemann, 1926; 62.

Fig. 30. Tycos recording sphygmotonomograph. Reproduced from: Halls Dally JF. High blood pressure: its variations and control, 2nd ed. London: W Heinemann, 1926; 64.
The standard mercury and aneroid sphygmomanometers which are the mainstay of clinical sphygmomanometry, have been improved over the years, but their basic design does not differ greatly from the early models. However, in recent years there has been considerable concern about the inaccuracy of blood pressure measurement (95). There have been many critical evaluations of the technique (96) and a series of recommendations for greater accuracy has been made by official bodies, such as the British Hypertension Society (97) and the American Heart Association (98). The sources of inaccuracy of blood pressure measurement have been reviewed elsewhere (99), but two sources of error are of historical importance in that they have influenced sphygmomanometer design, namely bladder size and observer error.

Inflatable bladder dimensions

Of the many controversial issues in hypertension few can rival that of determining the optimal bladder dimensions for a particular arm circumference. The problem is as old as the technique of blood pressure measurement itself. When Scipione Riva Rocci introduced the technique of cuff occlusion for the measurement of systolic blood pressure in 1896 (39), he used a very narrow cuff. Von Recklinghausen soon recognized that this was causing error and he recommended that the bladder should have a width of 12–13 cm (43). For the first quarter of this century it would seem
TABLE 1.  Recommended bladder dimensions

<table>
<thead>
<tr>
<th>Dimensions (cm)</th>
<th>Subject</th>
<th>Maximum arm circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 × 4</td>
<td>Small children</td>
<td>17 cm</td>
</tr>
<tr>
<td>18 × 8</td>
<td>Medium-sized children</td>
<td>26 cm</td>
</tr>
<tr>
<td>35 × 12.5</td>
<td>Grown children and adults</td>
<td>42 cm</td>
</tr>
</tbody>
</table>

Accurate readings may be obtained in adults with arm circumferences greater than 42 cm by placing a cuff with a 35 cm bladder so that the center of the bladder is over the brachial artery. Reprinted from Blood Pressure Measurement by permission of the British Medical Journal.

that sphygmomanometers were provided with bladders that completely encircled the arm (100) and, indeed, such was the recommendation of the World Health Organisation in 1959 (101). However, during the next decade or so manufacturers began to reduce bladder size without consideration of the clinical inaccuracy caused by such a modification (102). An unnecessary controversy, that has consumed much energy and research resources, has raged ever since. It is fair to say that a review of the sizable literature on the subject (99) often serves to confuse rather than clarify.

It is generally agreed that the width of the bladder is not as critical as the length, provided bladder length is adequate and the bladder is not excessively narrow. The overwhelming opinion from the literature is for bladders with greater lengths (32 – 42 cm) so that the arm is encircled by the bladder in most subjects; the British Hypertension Society (97) and the British Standards Institution (103) have each decided to recommend only 3 cuffs for routine clinical use, with the proviso that for very large arms care should be taken to ensure that the center of the bladder is placed over the brachial artery (Table I). This topic has been reviewed in depth by King (96) and Geddes (104).

Observer error

Blood pressure measurement by an observer using a standard mercury sphygmomanometer and stethoscope is subject to observer prejudice and terminal digit preference. These limitations can introduce error which is unacceptable for research work. Two devices have been designed specifically for research use — the random zero sphygmomanometer, which reduced observer prejudice, and the London School of Hygiene sphygmomanometer, which reduced both observer prejudice and terminal digit preference.

London School of Hygiene sphygmomanometer

The first such device to be introduced was the London School of Hygiene Sphygmomanometer (105). By means of a series of columns and plungers the observer records pressure by depressing the appropriate plunger at the end-points for systolic pressure and Phases IV and V diastolic pressure without having any means of knowing the pressure in the cuff (Fig. 32). The problems of terminal digit preference and
Fig. 32. London School of Hygiene sphygmomanometer. Photograph of model in the author's possession.
observer prejudice were thus removed and the instrument became popular in epidemiological and research studies for many years (99). Rather surprisingly it was accepted as the standard for blood pressure measurement without being subjected to validation. In 1982 a calibration error was demonstrated (106) which has not been rectified and the instrument is not now much used. The London School of Hygiene sphygmomanometer was modified by Nyberg (107) but this adaptation never became available for widespread use.

*Random-zero sphygmomanometer*

In 1963, Garrow described a 'zero-muddler for unprejudiced sphygmomanometry' (108) which was modified by Wright and Dore in 1970 (109) and produced commercially by Hawksley and Sons (Fig. 33). It is larger than a conventional sphygmomanometer and some 10 times more expensive. The manometer function is similar to

*Fig. 33.* Random-zero sphygmomanometer. Photograph of model in the author’s possession.
the mercury sphygmomanometer, but a wheel is spun before each measurement to adjust the zero to an unknown level. Once the blood pressure has been measured the level of zero may be determined and the pressure reading corrected. In this way observer prejudice is reduced but not digit preference. This device is generally accepted as the instrument of choice for epidemiological and research studies because it reduces observer bias and obscures digit preference, though the facility of the device to reduce terminal digit preference has been questioned (99). Because the random-zero sphygmomanometer is basically a mercury sphygmomanometer, its accuracy has been accepted rather uncritically and it has replaced the London School of Hygiene sphygmomanometer as the standard against which other devices are assessed (99). However, a number of recent studies have demonstrated that the instrument systematically gives lower readings than the standard mercury sphygmomanometer and it is no longer recommended in its present design for research and epidemiological studies (110).

Hoyt and Wolf modified the random-zero sphygmomanometer in 1984 (111), but, as with Nyberg's modification of the London School of Hygiene sphygmomanometer (107), it does not appear to have been developed commercially.

V. DEVELOPMENT OF AUTOMATED TECHNIQUES

However complex the evolution of sphygmomanometry may have been prior to the introduction of the Korotkov technique, the technological advances of the twentieth century have been such that many automated devices have been manufactured and a detailed history would be outside the compass of this review which will attempt only to indicate major developments.

Janeway had recognized the variability of blood pressure in 1904 and had stressed the importance of making repeated observations of blood pressure (112). In 1917 Bernard Fantus devised an automatic recorder consisting of an Erlanger oscillographic manometer which was capable of automatically recording blood pressure, but it was never used in clinical studies (113). In 1921, Marian Blankenhorn (1885 – 1957) described an instrument for measuring blood pressure both repeatedly and automatically. Essentially it consisted of a double Ludwig kymograph and electrical motor by which it was possible to control inflation from a pressurized air source. Blankenhorn, who was fascinated by the effects of sleep on blood pressure, used this device to observe the behavior of blood pressure during sleep and made the interesting observation that he had difficulty in differentiating the 20 mmHg fall in blood pressure that may occur in normal subjects when turning from the supine to lateral position from that which occurs with sleep (114). It is interesting to reflect on the importance these early workers in clinical sphygmomanometry attached to the physiological variations in blood pressure that occurred with sleep, and in 1900 Walden compared the effects of natural and hypnotic sleep on blood pressure (115).

Since Blankenhorn's innovative device there have been many attempts at designing accurate automated devices capable of recording blood pressure at pre-set intervals automatically. The majority of such devices depend on Korotkov sound detection with a microphone, or the detection of arterial blood flow by oscillometry or ultrasound. However, a variety of devices dependent on alternative mechanisms
have been developed in recent years; these include flush-dependent techniques, the
phase-shift method, infrasound recording, wideband external pulse recording, ple-
thysmography and tonometry, but as with other automated devices the results of
validation have often been disappointing.

*Palpatory technique*

The first attempts to assess systolic blood pressure were by estimating the amount
of digital pressure required to obliterate the radial or other pulse and many physi-
cians took such pride in this skill that they resented the introduction of the sphygmo-
manometer (59, 73). Palpation of systolic pressure is still recommended as a
preliminary technique in routine sphygmomanometry to exclude the presence of an
auscultatory gap (99). Segall has described the palpation of diastolic blood pressure
which he found accurate, but it never gained wide acceptance clinically (116). The
technique does have some practical relevance for observers with poor hearing and
is defended by Geddes (117).

*Korotkov sound detection*

With improving technology it is hardly surprising that manufacturers have attempt-
ted to design an automated device for routine clinical use. Indeed, the market for
such devices has grown substantially with the increasing popularity of home
measurement of blood pressure following the introduction of this technique by
Brown in 1930 (118) and subsequent studies by a number of workers (see Chapter
5). Quite apart from market considerations an accurate semi-automated device
would have the advantage of eliminating errors of interpretation together with
observer bias and terminal digit preference. A number of semi-automated devices
based on Korotkov sound detection are available (119 - 121). In the majority an
electronic microphone shielded from extraneous noise in the pressure cuff is used
to detect the Korotkov sounds and blood pressure may be recorded on a chart, or
indicated on a digital display. The microphones are sensitive to movement and fric-
tion, however, and may be difficult to place accurately. Manual or automatic infla-
tion and deflation, or both, may be available (99). Refinements, such as ECG
gating, whereby auditory signals from the artery are only recorded when a transmi-
ted pulse is anticipated, have helped to reduce the noise of artefactual sounds (122,
123). However, in spite of remarkable technological advances and production of an
array of devices sphygmomanometry has been bedevilled, as in the past, by inaccu-
acy which is unacceptable in clinical practice and at the time of writing a semi-
automated or automated device of proven accuracy is not available for the routine
clinical measurement of blood pressure (99). In fact, dramatic though technological
developments have been it must surely be a salutary indictment of biomedical
engineering that nearly a century after Riva-Rocci and Korotkov introduced the
technique of clinical sphygmomanometry, the only acceptable standard for blood
pressure measurement is a trained observer using a standard mercury sphygmo-
manometer and stethoscope (99).
Oscillometry

The oscillometric technique, which enjoyed a considerable vogue around the turn of the century, is now becoming popular again. Oscillometric detection is based on the principle that as cuff pressure decreases from above systolic to below diastolic pressure, oscillations in the bladder are transmitted to either a mercury or, more usually, an aneroid manometer or other recording system. Two cuffs are often employed for oscillometric measurement; the lower one acting as a sensing cuff is inflated to pressure well below systolic pressure and as the pressure in the upper cuff is decreased systolic pressure is registered by the appearance of the first oscillations in the distal cuff. The detection of diastolic pressure has been a source of controversy, but it is now accepted as being the point of abrupt decrease in amplitude of the maximum oscillations (124). The development of oscillometry has been well reviewed by Geddes (125).

Complex devices that record blood pressure automatically at pre-set intervals have been designed for intensive care units and theatres. Examples of such systems are the Dinamap (126) and Vita-Stat (127). Such devices may use two methods of measurement, most commonly Korotkov sound detection and oscillometry, but often the mode being used is not indicated and assessments of accuracy for each mode are sometimes not available from the manufacturers. Moreover, these units do not always lend themselves to independent assessment because of their complex design. Reports of accuracy from independent units, each using a different validation protocol, makes comparison of results difficult and it may be many years before there is sufficient evidence to enable prospective buyers to make a confident judgement (99).

Flush techniques

Gaertner used a flush method of measuring systolic pressure in the finger which was popular for a time (41), but the only lasting application of the flush technique has been in pediatrics for measuring blood pressure in neonates and small children. The technique is based on the principle that if an extremity, usually the foot, is made bloodless by wrapping it in a bandage and a distally inflated cuff is slowly deflated, the point of flushing of the extremity indicates systolic pressure (128). The technique has been rendered obsolete by newer methods of ultrasonic measurement.

Ultrasonic devices

Arterial wall motion may be detected by the change in frequency of reflected ultrasonic waves transmitted by a transducer positioned over the brachial artery. Changes in arterial wall movement are detected by changes in ultrasonic frequency at the point of systolic and diastolic pressures — the Doppler shift phenomenon (129). The technique is particularly suited for measuring blood pressure in neonates and states of shock (128, 130) in which Korotkov sound detection may be difficult, but the accuracy of the technique is dependent on accurate placement of the transducer. Two features make ultrasound particularly attractive: namely, it is applicable to infants as well as to adults, and it records pressure in hypotensive states (131).
Infrasonic devices

The infrasonic method of blood pressure measurement depends on the detection of very-low-frequency acoustic wave energy generated during movement of the arterial wall which is converted to an audible signal. Results with this technique generally have been disappointing (132, 133).

Impedance plethysmography

With impedance plethysmography changes in limb volume are detected by alterations in tissue impedance. During deflation of an upper arm cuff changes in impedance measured by two electrodes, placed on the skin of the forearm, are detected at the point where the pulse first appears below the cuff leading to a change in arm volume (134). This method, which has been used mostly in neonates, is generally restricted to detection of systolic pressure as measurement of diastolic pressure tends to be variable.

Tonometry

Tonometry means simply the measurement of force. It does not require the use of occluding cuffs, being based on the principle that displacement of a force-sensitive transducer over a superficial artery can be made linearly proportional to the arterial blood pressure (135). Tonometry can provide a continuous read-out of pulse pressure, but its application is greatly limited by the need for critical placement of the instrument as any displacement leads to marked fluctuations in recording amplitude necessitating repositioning and recalibration. A new application of tonometry utilizing multiple transducers in a single diaphragm may overcome many of the shortcomings of tonometry and the system will soon be marketed (136).

Finger blood pressure

The finger was first used by for measuring blood pressure by Marey in 1880 who attempted to measure pressure by oscilometry (37). In 1895, Mosso used all the fingers of one hand to amplify finger oscillations (38). Four years later Gaertner measured what he thought was mean blood pressure by observing the point of flushing during cuff deflation in a finger that had been made bloodless with an occluding ring (41, 42).

A number of finger measuring systems based on the detection of a volume changes in a digit by double cuff systems have been developed for clinical blood pressure measurement, but accuracy studies have yielded conflicting results (121, 137) and the techniques are subject to the problems caused by vasoconstriction. However, new finger measuring techniques are being developed for the measurement of ambulatory blood pressure and are described below.

Phase shift method

Various techniques have been developed to detect volume changes dependent on pulse wave velocity. The phase shift technique measures blood pressure by detecting
the time taken for blood to travel between 3 occluding cuffs — the phase shift —
as the pressure decreases in the cuffs (138). This interesting technique merits further
development.

*Wideband external pulse recording*

Recently Blank and colleagues, using a transducer with a wide frequency response,
have separated the external pulse recorded during cuff deflation into 3 components
which can be used to determine systolic and diastolic pressure (139).

Many of the innovative techniques referred to in this section hold promise for the
future, but the results of validation studies have often been disappointing. It is
essential that new instruments for measuring blood pressure are fully evaluated
before being introduced for clinical practice (140) if they are to gain a permanent
place in future reviews of the history of blood pressure measurement.

VI. AMBULATORY MEASUREMENT OF BLOOD PRESSURE

For not the first time in this review we must turn to Theodore Janeway, who, as
far back as 1904, drew attention to the variability of blood pressure and the striking
response to stresses, such as surgery, tobacco and anxiety (141). A quarter of a cen-
tury later Smirk and his colleagues attempted to assess blood pressure behavior in
the individual by measuring basal blood pressure (142), and in 1940 Ayman and
Goldshine showed that blood pressure measured at home was lower than in the
clinic (143). Using a non-invasive apparatus which employed a Gallavardin double
cuff, the late George Pickering and his group at Oxford showed for the first time
how constant and profound was the fall in blood pressure recorded during sleep.
They also demonstrated the fluctuations in pressure during the course of 24 hours
(144).

This system, which was not portable, did not permit measurement during unre-
stricted activity and Pickering's group went on to develop an ambulatory technique
whereby pressure could be measured directly from the brachial artery with a small
plastic catheter (145) (Fig. 34). The first intra-arterial ambulatory blood pressure
measurement was performed in Oxford in 1966 and the first publication reporting
blood pressure changes in unrestricted man was in 1969 (146) (see Chapter 16).

*Intra-arterial measurement of ambulatory blood pressure*

The Oxford system has been adopted by other centers to provide important infor-
mation on blood pressure behavior (147, 148). It soon became apparent that blood
pressure varied considerably in response to a variety of stresses which included the
presence of a doctor, nurse or technician (any one of which was capable of inducing
the orienting reflex or defense reaction (147, 149), lecturing, driving a motor car
(150), and having sexual intercourse (151). Furthermore, ambulatory measurement
made it possible to determine, not alone the blood-pressure-lowering efficacy of an-
tihypertensive drugs, but also their duration of action (152). Perhaps, most exciting-
Fig. 34. The Oxford intra-arterial system for 24-hour blood pressure measurement. Reproduced from: Pickering G. *High blood pressure, 2nd ed.* London: J & A Churchill, 1968; (facing p. 21).

ly of all, 24-hour ambulatory recordings of blood pressure provided sufficient data for the characterization of nocturnal blood pressure (153) and the diurnal pattern of blood pressure (154), a subject reviewed with characteristic clarity by Pickering in 1964 (155).

These studies, though offering new insights into blood pressure behavior, had little, if any, effect on clinical practice chiefly due to the limitations of invasive intra-arterial measurement, not least being the dangers inherent in the procedure (145, 156). Attention was turned, therefore, towards developing a device that would measure ambulatory blood pressure non-invasively. The early history of ambulatory blood pressure measurement has been reviewed by Pickering and Stott (145) and Horan and his colleagues (157).

**Non-invasive intermittent measurement of ambulatory blood pressure**

*Day-time ambulatory blood pressure*

In the 1960s a number of attempts were made to provide a non-invasive alternative to direct intra-arterial measurement of ambulatory blood pressure. These early
developments in the technique have been reviewed by Pickering (158). In 1962, two instruments were devised for measuring systolic pressure in a digital artery, but, as with all finger measuring devices, the problems associated with vasoconstriction limited their application. Two instruments using cuff inflation and Korotkov sounds were also developed at this time but were of limited application because of their size. A more portable system utilizing a Gallavardin double cuff and detecting the phase shift of pressure has already been referred to (144). In 1968, Schneider and his colleagues described a fully automatic portable blood pressure recorder which was reasonably accurate (159). None of these instruments was developed commercially and, therefore, never became established in clinical practice.

1962, Hinman and his colleagues described the first truly portable ambulatory system for the non-invasive measurement of blood pressure (160). The Remler Company of California developed this system commercially (161) (Fig. 35) and so began an important era in hypertension management, the effects of which are only now being fully appreciated; it has been used by a number of workers who validated its accuracy (162–165).

Fig. 35. The Remler ambulatory blood pressure recorder. Reproduced from: Kain HK, Hinman AT, Sokolow M. Arterial blood pressure measurements with a portable recorder in hypertensive patients. I. Variability and correlation with 'casual' pressures. Circulation 1964; 30: 882–892.
The Remler consisted of a battery-operated recorder worn by the patient, a cuff which was inflated by the patient at pre-determined intervals and a microphone strapped over the brachial artery. Blood pressures were recorded on a magnetic tape which could be later decoded and the pressure plotted over the period of recording (163). Because the device depended on inflation by the subject, recordings were confined to waking hours and rarely lasted more than 12 – 14 hours. Moreover, unlike direct intra-arterial ambulatory blood pressure, the Remler system, in common with most of its successors, measured blood pressure intermittently at pre-set intervals and not continuously as with the direct technique and subjects were required to pause in their activities so that the arm may be held steady during recording of pressure. Moreover, the Remler system required the subject to inflate the cuff at pre-determined intervals. These disadvantages were offset to a large extent, however, by the safety of non-invasive measurement.

As with intra-arterial measurement, the Remler system provided new insights into blood pressure behavior (166) and new data on antihypertensive drug efficacy and duration of effect (167, 168). Among the most important aspects of hypertension studied with the Remler was the demonstration by Sokolow and his colleagues that ambulatory blood pressure was a better predictor of morbidity and mortality than casual office pressure (169, 170).

Twenty-four-hour ambulatory blood pressure

With the development of compact pumps and solid-state memory systems, the Remler system was replaced by devices capable of automatically inflating the cuff and providing pressures intermittently over 24 hours. However, despite the many technological developments in equipment design, the Remler remains unique in having possessed one outstanding merit, namely the facility that enabled the operator to listen to the recordings on tape and thereby distinguish between Korotkov sounds and artefactual noise (163).

In 1979, Harshfield and his colleagues at Cornell validated the Del Mar Avionics Pressurometer II Ambulatory ECG and Blood Pressure Recording System (171). This system, which was fully automated, permitted the measurement of blood pressure throughout the 24 hours non-invasively. Early models were bulky and noisy, but the Del Mar system has been modified and made more portable over the years. By providing a non-invasive profile of blood pressures over the 24-hour period, it has been used extensively in assessing circadian patterns in normotensive (172) and hypertensive subjects (173) and in demonstrating the duration of action of antihypertensive drugs (157). The Avionics system was followed by a number of automated devices for the measurement of 24-hour blood pressure (174). Systems, such as the latest SpaceLabs device, the 90207 (Fig. 36), are pocket-sized with an almost noiseless pump (175). Some systems measure blood pressure by Korotkov sound detection, with or without ECG gating, and others use oscillometry (174). These instruments are expensive and strict accuracy criteria are being demanded from manufacturers (176).

Being non-invasive and almost completely free of adverse effects, these automated systems, capable of giving accurate profiles of blood pressure behavior over 24 hours, have found much wider use in research and clinical practice than was
ever possible with invasive techniques. The concept of white coat hypertension, the phenomenon whereby blood pressure recorded by doctors and nurses is much higher than ambulatory day-time pressure, a theme so strikingly developed by Sir George Pickering in the 1960s in Oxford, has been elucidated by his son Professor Thomas Pickering at Cornell (177). Recently profiles of 24-hour blood pressure in normal subjects have been characterized in population studies (178). It may now be anticipated that ambulatory blood pressure will become indispensable in the assessment of patients with elevated blood pressure (179).

Non-invasive continuous measurement of ambulatory blood pressure

The main disadvantages of the above systems are that they only provide intermittent measurement of 24-hour blood pressure and that the subject has to cease activity during the measurement of blood pressure. Though intermittent blood pressures give circadian blood pressure patterns which are surprisingly close to intra-arterial pressures (180), there is a limit to the number of pre-set measurements a subject can be expected to tolerate and, moreover, there comes a point at which intermittent measurements interfere with normal ambulatory activity. In practice, therefore, ambulatory measurements are usually made at 15-minute or 30-minute intervals. The disturbing effect of cuff inflation on sleep has also to be considered with these systems and their accuracy during exercise has been questioned (181). The next advance in blood pressure measurement is likely to be the development of accurate systems that will provide continuous 24-hour blood pressure allowing detailed waveform scrutiny and beat-to-beat analysis — in short, the equivalent of direct intra-arterial measurement without the inherent dangers of invasive catheterization.

In 1968, Peñáz patented a servo-plethysmomanometer based on the vascular
unloading principle using a light source and photocell in a finger cuff (182). In 1973, he presented the technique at Dresden (183). The cuff of the instrument is inflated above systolic pressure and deflated until maximum unloading of the arterial wall occurs at the point of mean arterial pressure. This signal is used as a reference standard to vary cuff pressure with the pulse so that maximum unloading is maintained throughout arterial pressure recording. Peñáz's technique has been modified by Wesseling in The Netherlands (184), and manufactured as the Finapres (FINger arterial PRESSure). This device may prove to be an acceptable alternative to direct intra-arterial measurement for the continuous recording of blood pressure (185, 186) (see Chapter 11).

Another technique based on the Peñáz principle of vascular unloading has been described by Yamakoshi and colleagues (187). Using a hydraulic servo-control system, counterpressure is applied to the finger to equalize arterial pressure and arterial pressure is indirectly estimated by measuring the counterpressure. More recently Yamakoshi and his colleagues have elaborated on this technique describing two methods of measuring blood pressure continuously utilizing arterial elastic properties — a volume-oscillometric and a volume-compensation method (188), each based on the vascular unloading principle of Peñáz (183). These techniques may also prove to be an alternative means of obtaining continuous blood pressure recordings non-invasively.

Technological advances must soon provide accurate alternatives to the traditional techniques of blood pressure measurement. Recently, the Association for the Advancement of Medical Instrumentation (189) and the British Hypertension Society (176) have produced strict criteria for the evaluation of blood-pressure-measuring devices, most especially ambulatory systems. It will be necessary, therefore, in future for manufacturers to provide evidence of independent validation of the many innovative techniques which the future promises. Writing in 1987, Garrett and Kaplan stated that 'ambulatory blood pressure monitoring on a 24-hour basis is an idea whose time has come' (190). This is an appropriate note on which to close this section on the history of ambulatory measurement signalling, as it does, the end of an era and the beginning of a new epoch, that in which assessment of the individual with suspected blood pressure elevation will no longer be dependent on isolated measurements made under strange circumstances but dependent rather on evaluation of a 24-hour profile of blood pressure behavior in more natural surroundings than the hospital clinic or family doctor's office. The future holds promise, moreover, for more rational selection of antihypertensive drug therapy so that treatment will be evaluated according to the individual pattern of diurnal blood pressure.

Historically, it is of interest to note that ambulatory measurement had its origins in a non-invasive technique, followed by an invasive era during which much valuable information on blood pressure behavior was gathered, and that with developments in technology the technique has returned to non-invasive methodology.

VII. ENVOL

It is just over 250 years since the Reverend Hales discovered blood pressure and provided the crude principles of direct measurement (3). It is a little over 100 years since
von Basch (830) and Riva-Rocci (39) devised instruments enabling the measurement of systolic blood pressure in clinical practice and just 85 years since Nicolai Korotkov (61) introduced the auscultatory technique of blood pressure measurement which remains the ‘gold standard’ of measurement to this day.

This review commenced in critical wonderment at the lapse of a century between Harvey’s discovery of the circulation (2) and Hales’s description of blood pressure (3) and the similar delay before blood pressure measurement was applied to man. These lacunae in the development of scientific thought can be excused, at least to some extent, by the inadequacy of the technical facilities at the disposal of these
pioneering scientists. The discovery of rubber, for example, by making possible a secure connection between pressure-detecting systems and a manometer, did more to advance blood pressure measurement than did the development of scientific ideas.

No such reasoning can vindicate the paucity of development in blood pressure measurement in this century, most especially in the latter quarter, a period which future historians will refer to as 'the technological age'. It becomes evident from a historical review, such as this, that the indifference of practitioners of blood pressure measurement (for the greater part doctors, a significant number of whom would wish to be judged as 'scientists') to the accuracy of the scientific principles of methodology, so carefully enunciated by early researchers, has resulted in those principles being relaxed rather than being developed in the light of advances in knowledge. That the past decade should witness a revival of the criteria so clearly laid down by Faught (86) and Janeway (47) in the early years of the century, or that resources need be expended on persuading manufacturers to restore the dimensions of the inflatable bladder to those which had been accepted as integral to the technique in the first half of the century must surely place a serious question mark against scientific reasoning: if scientific vigilance had been exercised, this eventuality need never have been.

Critical though historical analysis may force us to be of our failure to preserve the fundamental aspects of measurement and to capitalize on the elaborate technology (to which we are heirs) to improve the procedure, the sternest historical indictment of future generations will be directed at our insistence in permitting isolated blood pressure measurements to dictate diagnostic and management policies in hypertension in the light of an abundance of evidence, beginning with Janeway's studies in 1904 (141), and emphasized by Pickering's (Fig. 37) Oxford group in the 1960s (145), showing the variability of blood pressure and the effect of doctors themselves on the very quantity they were attempting to measure. How many have been subjected to unnecessary or inappropriate therapy, and continue to be mismanaged at the time of writing, is a matter of such concern that we must bow in gratitude to those of our predecessors who perceived the way forward so clearly and to acknowledge that the lessons of history can alert us to our ineptitudes and direct our future endeavors.

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2. Technical aspects of blood pressure measurement

E.B. Raftery

The matters discussed in this chapter (measurement of arterial pressure in man) leave the writer with a sense of chastened humility. The methods we use to estimate blood pressure are obviously of limited accuracy, and the values we seek to record, systolic and diastolic pressures, have themselves an elusive quality.

(Sir George Pickering, 1955)

Before one attempts to measure something, it would seem logical to define what it is that is going to be measured. Nevertheless, despite the many volumes written about blood pressure, no author has yet defined what it is. Even the great physiologist Carl Wiggers (1) failed to define what he was measuring, although he took considerable pains in describing how to set about measuring it.

Pressure is defined as force per unit area. Since the medical interest in blood pressure centers around the age-old observation that there is a relationship between the perceived tension of the pulse palpated at the wrist and longevity (2), it would seem reasonable to define blood pressure as the lateral forces exerted on the wall of an artery when the left ventricle ejects a volume of blood into a filled system of elastic tubes. And it is evident from the many descriptions of methods of measuring blood pressure that this is what the authors had in mind.

The earliest techniques to be applied were direct, and involved surgical exposure of blood vessels. Clearly these methods could not be applied to man, and much ingenuity has been expended in devising non-invasive methods of estimating blood pressure. The purpose of this chapter is to review the principles underlying some of these invasive and non-invasive techniques.

1. PHYSIOLOGICAL PRINCIPLES

Pressure is commonly measured in millimeters of mercury, referred to atmospheric pressure as the zero point. This unit was first introduced by Poiseuille in 1828 (3)
(while he was still a medical student) and has stood the test of time and attempts to replace it with other units such as the torr (1 torr = 1 mmHg) and the pascal (1 Pa = 7.5 mmHg). Since pressure in the arterial circulation is generated by the left ventricle it is obvious that each contraction will generate its own pressures and that no two beats will be the same. In other words, arterial pressure, no matter how it is measured, is a continuous variable and no two measurements will be the same. Therefore any measurement of blood pressure by any technique will be relevant only to the time at which that measurement was taken, and cannot be extrapolated to any other point in time.

The events of the cardiac cycle in the arterial circuit have been described as a pressure pulse (Fig. 1), the components of which have been the subject of intense observation and investigation since the beginning of the century. The pressure pulse has two limbs: the ascending (or anacrotic) and the descending (dicrotic). It also has a zenith (systolic) and a nadir (diastolic). Systolic pressure is largely determined by the force and volume of blood ejected by the left ventricle into the aorta, and diastolic pressure by the resistance to volume displacement presented by the arterial tree. It is well known that the greatest pressure drop in the arterial circuit occurs at the level of the peripheral arteriole, which therefore is the prime regulator of diastolic pressure. The shape of the pressure pulse changes as it traverses the arterial tree, largely because of superimposition of waves reflected back from the periphery (Fig. 2), particularly from points of branching.

Transmural pressure across the wall of an artery tells us little about the force or vigor of left ventricular contraction; the pressure gradient between the aorta and the brachial artery is only a few millimeters of mercury while the transmural pressure may be measured in hundreds of millimeters. Furthermore, pressure differences between other parts of the arterial tree may be very large and it should be remembered that we use the brachial artery to measure 'blood pressure' merely as a matter of

\[
\text{Systolic Pressure} \quad \text{Dicrotic} \quad \text{Mean Pressure} \quad \text{Diastolic Pressure}
\]

\[
\text{Pulse Pressure} \quad \text{Anacrotic}
\]

Fig. 1. Schematic presentation of the pressure pulse to illustrate the 3 numerical representations of blood pressure: systolic, diastolic, and mean. Many other variables such as dp/dt of the upstroke and stroke output may be derived from the pressure pulse if it is accurately inscribed.
Fig. 2. Changes in the shape of the pressure pulse as a function of distance from the valve in the aorta of the dog (numbers are centimeters from the arch). There is an apparent increase in systolic pressure with distance, but the area under each curve (i.e. total energy per pressure pulse) remains constant. Modified from: Hamilton and Dow. *Am J Physiol* 1939; 125: 48.

convenience. The arm is readily accessible and conveniently close to the heart, so that zero-finding is not a great problem. Caro and colleagues (4) have made the point that a transmural pressure of 200 mmHg may be perfectly normal in the arteries of a dependent leg.

It is also worth remembering that the palpated pulse is not identical to the recorded pressure pulse. Arterial blood velocity is of the order of 0.5 m/s while the pressure wave travels at 4–5 m/s, and the quality of the palpable pulse is more a function of the properties of the arterial wall than events inside the vessel. Furthermore, direct pressures taken from catheter systems facing upstream in an artery are not measuring lateral forces. On the contrary, they are measuring the forces at the leading edge of the pressure wave, and although these will be very similar to the lateral forces, they are by no means identical.

The available methods for measuring arterial blood pressure fall into two broad groups: direct and indirect.

**II. DIRECT METHODS**

There has been a steady and rapid evolution of the methods of direct registration of the arterial blood pressure over the past 90 years. The direct equipment responds rapidly and accurately to changes in pressure and available techniques are now highly sophisticated and allow precise description of each pressure pulse together
with a clear definition of its accuracy and limitations. This is in stark contrast to the indirect techniques. However, it should be remembered that a physical description of any direct technique should include all components, including the apparatus used to produce the final product, be it graphical or numerical. A wonderful transducer attached to a long and curvaceous catheter with doubtful frequency characteristics will not perform as well as the transducer alone.

The early physiologists measured lateral forces by inserting a brass T-tube into the vessel and attaching their measuring instruments to the vertical bar. This is seldom done nowadays, and it is more usual to insert a fluid-filled catheter which faces upstream. These systems are clearly not measuring the same set of forces.

A detailed review of direct methods that have been used in the past would not be appropriate here, but it should always be remembered that the results obtained with cumbersome and often rather 'quaint' apparatus by the early physiologists were rigidly controlled for quality. The observations made by Ludwig, Marey, Fick, Wiggers and many others are as valid today as they were then. However, the ease and accuracy of interpretation were greatly improved by the introduction of the mechano-optical and electrical systems which superceded the mercury-in-U-tube. The latter produced records which were distorted because the high inertia of the mercury had a pronounced damping effect (see later) such that maxima and minima or even mean pressure were the best that they could achieve.

The desirable components of a direct measuring system depend entirely on the use for which it is intended. The requirements of the physiologist conducting detailed and carefully controlled experiments are different from those of the clinical cardiologist conducting a routine coronary arteriogram. However, some generalizations are possible and each system requires 3 components: an input, a processor, and an output.

The input system consists of a fluid-filled catheter with a transducer attached to the proximal end, or a catheter with a transducer at the tip. The catheter may be inserted into the vessel by any one of a variety of techniques, of which the percutaneous approach under local anesthesia is the commonest. The wider, shorter, and more rigid the catheter, the greater the fidelity of the signal. The catheter-tip manometer is the best design for high fidelity, but is of limited value because the zero point cannot be determined during recordings, and the degree of drift can only be assessed by calibration before and after insertion (5). The transducer is the crucial element in the input system, since it senses the pressure changes and converts them into electrical signals. Many different designs are available, but all consist essentially of a stiff diaphragm that is in contact with the fluid in the catheter. To this is attached a displacement element, which may be one arm of a Wheatstone bridge, or a soft metal bar set in a magnetic field. Movement of this element generates an electrical signal, the magnitude of which has a linear relationship to the degree of displacement. Many such transducers are commercially available and their output specifications are universal. It should be borne in mind that the diaphragm is the most essential part of these instruments, and care should be taken to match its characteristics to the task in hand. High-pressure events call for a different diaphragm than low-pressure events.

The signal from the transducer passes to the electronic package where it is processed by the pre-amplifier to provide a bigger signal. This is a crucial stage in the
signal processing because of the possibility of band-width filtering to smooth the outline of the eventual signal (see later). The pre-amplifier should offer fidelity from 0–50 Hz, but this means that systolic overshoot or ‘ringing’ from underdamped hydraulic systems will also be faithfully reproduced. Filtering means a degree of lost information, and the decision to filter must rest with the person who is making the recording and be determined by its purpose. The pre-amplifier signal, whether processed or not, is passed to a bigger amplifier for a final boost to reach the power levels required to drive the third leg of the system: the recording device.

The number and variety of these devices is legion, ranging from direct-writing ink recorders to magnetic tape, and all that can be said in this context is that a good working knowledge of the physical characteristics of the recorder is again essential if the quality of the data is to match the reason for the recording.

It is obvious that blood circulates as an oscillating system of wave forms. In order to record these wave forms accurately, the recording system has to be able to match the oscillations coming from the arterial system faithfully and without distortion. The most important sources of error in all direct systems lie at the input end. The catheter may be a long tube with semielastic plastic walls, filled with saline which has a tendency to cavitation if it has not been carefully deoxygenated, or has air-bubbles trapped somewhere in the system. This may be connected to the transducer by yet another long plastic tube. Some understanding of the possible distortions that can be produced by a mismatch of physical characteristics is essential to the interpretation of all direct pressure recordings.

![Underdamped](image_url)

![Overdamped](image_url)

![Optimally damped](image_url)

*Fig. 3.* Schematic representations of the response of a catheter/transducer/recorder system to the sudden imposition and release of a pressure (square-wave response). If the system is underdamped, it will tend to resonate around its natural frequency (‘ringing’). If it is overdamped, the rise and fall of the signal will be slow and blurred. Optimal damping is characterized by a sharp rise and fall with a single oscillation at both ends.
All systems have a natural frequency of oscillation around which a minimal input of energy produces a maximal response. The natural frequency is determined by the springiness (or capacitance), and the mass (or iner- tance) of the system. Any oscillating system will eventually grind to a halt because friction between the particles (generating heat) will eventually deprive it of energy. ‘Damping’ is a measure of the frictional force acting in opposition to movement of mass in an oscillating system. It is self-evident that an input system that has little damping will tend to oscillate around its natural frequency. This could result in exaggerated pressure pulses. Similarly, a high degree of damping would result in erroneously low pressure pulses. An optimally-damped system is one which when displaced reverts rapidly, with only a slight oscillation, to its natural position (Fig. 3). Testing of such a system with a sine-wave generator should show a flat (i.e. constant) output up to 67% of the undamped natural frequency, with a sharp fall in output after this point (Fig. 4). Damping can be expressed numerically (6) according to the formula:

$$\beta = 4\mu/r^3\sqrt{l/\pi E}$$

where $\mu =$ viscosity, $l =$ length of tubing, $r =$ radius of tubing, $E =$ stiffness (change in pressure/change in volume). Some authors recommend a damping factor of 0.707 and others 0.64 as optimal. Damping may be achieved by physical or by electrical methods, but inevitably leads to other distortions. Ideally, the system should be constructed so that resonant frequencies are well beyond the range of interest, but this is impossible with hydraulic connecting systems, and some degree of damping must be used.

Each pressure pulse can be characterized as the sum of a number of sine-waves, each with its own characteristic frequency. The recording system will respond more
readily to frequencies near its natural frequency than to others, with the result that registration of some frequencies will be delayed over others. This phenomenon is called ‘phase shift’, and is seen particularly in damped systems. Fortunately, it is of very little significance in anything but work involving the precise timing of events in the cardiac cycle or the shape of the pressure pulse (which may be distorted by phase shift) (Fig. 5).

All of these physical characteristics of the direct pressure pulse can be, and should be, tested by two relatively simple techniques. The first is the square-wave test. This involves sudden application and removal of a pressure increment to the system and faithful recording of its response (Fig. 3). The frequency of the observed oscillation will indicate the resonant frequency of the system, and the amplitude the degree of damping (6). The complementary technique is a sine-wave generator: a fluid-filled chamber with a diaphragm fixed to a piston which will generate waves of known frequency and amplitude in the whole system while the pressure output is measured continuously by a strain gauge. The response of the system should be flat to 8 – 10 Hz for accurate pressure recording (Fig. 4). It must be emphasized that a description of the physical characteristics must embrace the whole system and not be confined to examination of the transducer and other electronic components. Furthermore, if the aim is precision, then they must be repeated for every experiment. If the aim is approximation, then the system should be examined at least once a year!

Fig. 5. Simultaneous recordings from the same part of a dog aorta, comparing the signal from a high-fidelity catheter-tip displacement manometer (Millar, flat to 1000 cps), a displacement manometer attached to a short length of fluid-filled tubing (Akers) and a complete recording system (Oxford Mark II). Note the low-frequency ‘noise’ which distorts the shape of the pressure pulse recorded from the Oxford system. This is due to phase shift of some frequencies induced by the tape recorder which captures the signal in this system. Calibrations and recording speed differ because simultaneous recording on a single system was not technically possible. While there is no significant loss of systolic and diastolic points, the shape of the curve is not accurate enough for precise timing of events.
III. INDIRECT METHODS

It should be clearly recognised that arterial pressure cannot be measured with precision by means of sphygmomanometers.

(Recommendation, American Heart Association Committee, 1951)

From the very beginning, the indirect techniques for measuring blood pressure have employed some method for occluding the artery under investigation and observing the pressure required to do so. The introduction of a pneumatic cuff to occlude the brachial artery by Riva-Rocci in 1896 (7) and Hill and Barnard in 1897 (8) revolutionized the known techniques, and the system was rapidly refined to produce the palpatory and flush methods. However, neither allowed anything more than an estimate of systolic pressure.

Many observers noted that deflation of pneumatic arm cuffs was associated with oscillations of pressure within the cuff, and it became apparent that these bore a relationship to systolic and diastolic pressure in the artery. In this way the oscillometric method for indirect measurement of blood pressure was conceived (Fig. 6).

When a pneumatic cuff is inflated around the arm to above systolic pressure, oscillation can still be recorded from the cuff. These oscillations reflect pulsation in the occluded artery above the cuff. When the cuff is deflated, there is a sudden increase in the amplitude of oscillation in the cuff as blood spurts through the partially opened artery. This point coincides well with systolic pressure. As deflation progresses, these oscillations steadily increase in amplitude to a maximum and then begin to decrease. There comes a point at which there is an abrupt decrease in the

![Diagram](image)

*Fig. 6. The oscillometric method for indirect recording of blood pressure. As with the Riva-Rocci/Korotkov method, the diastolic point is indeterminate. Furthermore, the oscillations seldom follow such a precise pattern.*
large oscillations, and this point was thought to coincide with diastolic pressure. These criteria were readily accepted by clinicians at the beginning of the century, but experience showed that the abrupt increase in oscillations was not always clear, and neither was the diastolic end-point. There were often two maxima and many other oscillatory phenomena which could not readily be explained. Because of this, the method fell into disuse and very few controlled validation studies with modern equipment have been performed. Unfortunately, the technique is now in renaissance because the manufacturers of semi-automatic ambulatory blood pressure monitoring equipment have discovered that it is easier to produce artefact-free recordings with oscillometry than with Korotkov sounds, and that the algorithms for automatic analysis are also easier to design. The physicians who use this equipment now find themselves in the same position as their predecessors in 1905: using measurements made by a doubtful technique which has never been properly validated.

The reason for the eclipse of the oscillometric method was the description of the Korotkov sounds in 1905 (9). This method was not readily accepted and it was subjected to considerable experimental scrutiny, but once it was realized that it was at least as accurate as the oscillometric method, and probably more so, it was universally adopted, and for the past 60 years has been the standard method for recording blood pressure in the human subject.

The apparatus which is used today (Fig. 7) consists of a cuff which encloses an inflatable bladder, which can be wrapped around the arm. The bladder is inflated by means of a small hand-pump, until the pulse at the wrist disappears. The brachial artery collapses into a ribbon-like structure with marked intimal corrugations (10). The cuff is then allowed to deflate while the observer listens over the brachial artery below the cuff, and the pressure within the bladder is monitored by a mercury-in-glass or by an anaeroid manometer. When the pressure in the artery above the cuff
starts to exceed the pressure within the bladder, the critical opening pressure of the occluded vessel is exceeded, and partial opening of the vessel below the cuff occurs with each pulse. The transverse section of the vessel expands to an ovoid with highly turbulent flow, vibrating the tissues around the vessel. It then collapses again. The vibrations are in the auditory range and this event is accompanied by the appearance of sound (Korotkov I), and equates to systolic blood pressure. As deflation continues, each pressure pulse achieves greater opening of the occluded vessel until a point is reached when the vessel remains partially open throughout each cardiac cycle, but flow continues to be turbulent. The critical opening pressure of the vessel has been exceeded in diastole, and when this happens, the quality of each sound changes with loss of higher frequency components (Korotkov IV; ‘muffling’). This point equates to diastolic pressure. As deflation continues, there comes a point at which the deflated vessel remains fully open throughout each cycle, laminar flow is established, and vibrations disappear together with sound (Korotkov V). There is still considerable controversy whether Korotkov IV or V properly represents diastolic pressure (11), but, for the sake of convenience, V is usually taken. This is not a satisfactory state of affairs. The difference between Phase IV and Phase V is usually so small as to have no practical significance. On the other hand, Phase IV is theoretically correct, and using this point as the true measure of diastole allows for the not infrequent situation of sounds which persist down to zero cuff pressures. This situation classically occurs in high cardiac output states such as pregnancy and high fever. Thus the technique gives an estimate of systolic and diastolic blood pressure over a minimum of 15 beats and under conditions where the subject is still and in a standardized position while the procedure goes forward.

Aneroid manometers are seldom used nowadays, because the vacuum between the diaphragms is hard to maintain, and the mechanical moving parts require regular lubrication. Regular calibration against a mercury column is essential. In contrast, the mercury-in-glass manometers are reliable and easily maintained, provided the system is cleaned and degreased every 6 months.

The contrast between the direct and indirect methods of measuring blood pressure has attracted much attention over the years. Because the direct method has obvious advantages of sensitivity and accuracy, it has been adopted as the standard against which to judge the indirect method. The first comparison of this kind was performed by Wolf and von Bonsdorff in 1931 (12) and there have been many such comparisons since (13).

In all of these published comparisons, it is assumed that the direct technique is providing a standard by which the indirect technique must be judged. This cannot be completely justified, because the indirect technique is attempting to measure the lateral forces on the wall of the brachial artery, while the direct technique is measuring forces at the leading edge of the pressure wave moving down the column of blood in the artery. The two are bound to be similar, but could hardly be expected to be the same. Thus the consistent demonstration of a high degree of correlation should cause no surprise, but there should be a systematic difference between the two sets of results. This ideal is seldom approached because most observers have used one arm for the direct, and the other for the indirect, measurement. Furthermore, they have assumed that the direct technique is perfect, and take no account of phenomena such as damping which can significantly distort the direct measure-
ment. Hence the almost universal failure to publish details of the physical characteristics of the apparatus used for direct measurement.

Only one published study has compared the two techniques in the same arm at the same time, and also gave details of the frequency characteristics of the direct apparatus to justify the accuracy of the method (13). This was performed in females of a limited age range, but is still the only study in which comparisons were made under ideal conditions for both methods. The results (Fig. 8) showed the expected close correlation between the two methods, but also showed considerable individual variations which appeared to be random and were certainly not systematic. The fact that systolic pressure may deviate by as much as ± 24 mmHg and diastolic pressure by ± 16 mmHg under ideal conditions must provoke thought about the intrinsic accuracy of the indirect method.

The list of possible reasons for these random discrepancies is very impressive:

A. Cuff  Five features of the bladder design and application are known to produce errors. Firstly, the evidence suggests that the best results are obtained if the bladder completely encircles the arm (14) and yet this is never the case with commercially available equipment. Secondly, failure to ensure that the bladder is placed over the artery can render a measurement completely invalid. Thirdly, the width of the bladder is standardized at 12 cm while the evidence suggests that the width should vary with the arm diameter (× 1.2 cm) or circumference (40%) so that the appropriate cuff can be chosen for the appropriate member (15). Fourthly, a close fit of the cuff is essential if pressure is to be transmitted uniformly to the subcutaneous tissues (16). Finally, the shape of the cuff can be critical, particularly in obese subjects (17).

Fig. 8. Comparison of direct and indirect blood pressures taken from the same brachial arteries at the same time under ideal conditions by well-trained observers. In each case, the line is the line of identity. While there is a close correlation (as would be expected), there is still considerable scatter and the indirect technique can be discrepant from the direct by as much as ± 24 mmHg systolic and ± 16 mmHg diastolic. There is no explanation for these random discrepancies. Reproduced from: Raftery EB, Ward AP. Cardiovasc, Res 1968; 2: 210–218.
B. Manometer The rates of inflation and deflation are known to affect the readings obtained. Slow inflation rates may lead to venous congestion which is known to affect the timing and quality of Korotkov sounds. The recommended deflation rate of 2 – 3 mmHg/s is seldom observed with any accuracy, and there are the problems of systematic error, observer bias and digit preference (18, 19) which may well introduce further errors. These may be partially compensated by using special instruments, but these are rarely in routine use. Two specially-designed mercury manometers are available. The first is the London School of Hygiene sphygmomanometer (18) which can be used with a standard cuff. It includes an automatic inflation device which taps a cylinder of compressed carbon dioxide and deflates at a constant rate of 3 mmHg/s. Cuff pressure is reflected on 3 mercury-in-glass columns which are hidden from the operator, who auscultates the brachial artery with the diaphragm of a standard stethoscope. The operator stops the descent of each column by pressing buttons on the front of the instrument when his ears register Korotkov I, IV and V. The columns have a scale of arbitrary numbers and at the end of each recording the height of mercury in each is noted. The scale is later calibrated against a mercury-in-glass manometer and each number converted to mmHg. This instrument is an excellent piece of design which should eliminate the problems of observer bias and digit preference, but it is very bulky and heavy. Furthermore, it has been shown to reduce but not eliminate digit preference (19) and a calibration error has been discovered (20) but not corrected.

The second is the so-called Hawkesley zero-muddling manometer (21). This looks like a conventional mercury-in-glass instrument and can be used as such. However, it has a wheel which is spun before each measurement to adjust the zero to an unknown level which affects the scale, reading in mmHg. This unknown zero level is determined afterwards, so that the pressure reading can be corrected. Cuff inflation is completely conventional, but the deflation rate can be controlled and regulated by a needle valve. This instrument has the great advantages of simplicity, lightness and portability, and it certainly reduces observer bias (22); however, it is still open to digit preference since the measurer must still correlate his ear and eye to the numbered scale (23, 24). Furthermore, the instrument systematically under-reads the mercury-in-glass sphygmomanometer (25 – 29) and careful servicing is essential to maintain accuracy (26).

There are major disadvantages associated with these instruments: they can only be used for one-off readings in carefully defined circumstances and in the setting of a laboratory or outpatient clinic; they are very difficult to use for studies of blood pressure changes during dynamic exercise; and consistent results depend the same observer on each occasion following a rigid routine. Furthermore, they are very expensive.

Finally, servicing of the equipment is a vital factor — dust in the inflation bulb or in the mercury column can further compound an error.

C. Auscultation While it is generally agreed that the first appearance of sound (Korotkov I) gives a good estimate of systolic pressure, there is still no definitive evidence on the correct auscultatory point for diastolic pressure. This point has already been discussed, but it is worth noting that roughly 5% of individuals have marked silent intervals during the course of cuff deflation. Ragan and Bordley (30)
showed that a silent interval can be induced by a slow rate of inflation, but this is not always the case and the unpredictability of these phenomena must be a factor in further discrepancies.

D. The artery  It is well-known that there may be differences between the two arms, and although this can be avoided by always using the right arm, it is still a possible source of error. Arteriosclerotic changes in the wall of the artery quite certainly influence the transmission of sound: hence the pseudo-hypertension described by Osler at the turn of the century (31).

How many other sources of error exist which have yet to be defined, remains a problem. Whatever they may be, the indirect technique can only be described as potentially inaccurate, and so slow-moving as to be limited in its reliability. Furthermore, the indirect technique may be rendered even more inaccurate by the ‘alerting reaction’ vividly described by Pickering (32) and now given a variety of other names such as ‘white-coat hypertension’. This phenomenon is characterized by a smart rise in blood pressure at the approach of a doctor (Fig. 9). The indirect method is incapable of identifying or quantifying the alerting reaction, which has been elegantly demonstrated by the direct technique. It has been shown that nurses elicit a smaller rise in pressure than doctors (33), but it is not possible to predict which subject will react in this way or the degree of the reaction.

IV. SEMI-AUTOMATIC MACHINES

It will be apparent to the reader that a common thread which runs through the indirect methods so far described is a pneumatic cuff, which can be inflated to occlude

![Graph](image)

*Fig. 9. A continuous recording of ambulatory intra-arterial blood pressure taken from a hypertensive subject. Note the marked variation in the systolic and diastolic pressures, and the sharp rise in response to the approach of a doctor in a white coat. The vertical dotted line is a calibration signal.*
the brachial artery in the arm, and some method of detecting motion in the wall of
the occluded artery when the cuff is deflated. This forms the basis for both the
oscillometric and the auscultatory methods. Many other techniques have been in-
troduced, and each is hailed as a ‘new’ method. But in every case the principle has
been the same, and the only difference is the method used to detect arterial wall mo-
tion. These instruments have a place in specialized areas such as small children and
the patient with very low blood pressure, but they all suffer from the same con-
straints as the auscultatory method, and claims for increased accuracy and precision
should be viewed with some caution.

Sound detectors

In these instruments automatic cuff inflation and deflation is linked with a piezo-
electric crystal placed over the brachial artery and shielded from extraneous noise.
The signal from the microphone is compared with the pressure in the cuff (usually
measured by means of small strain gauge) and a display system indicates pressure
at Korotkov I, IV and/or V. The display systems can vary from a chart recording
to flashing colored lights. There are at least 15 machines of this type on the market,
some with manual inflation and some with automatic inflation/deflation systems.
Few published studies on the accuracy of these instruments are available, but most
agree that they are less reliable than the basic stethoscope and mercury manometer
(26, 34). The microphones are notoriously sensitive to movement and friction of all
kinds, are difficult to place accurately (particularly when built into a cuff), and are
nothing like as good at detecting Phase IV Korotkov as the human ear. There is no
official requirement for these instruments to be properly assessed before their
release onto the market and the manufacturers’ claims are often misleading (35).

Wall movement detectors

Here the Korotkov sounds have been replaced by detection of initial movement,
‘flutter’, and finally distension of the arterial wall by means of an echo-sounding
device. The commonest method used is ultrasound. These instruments are heavy and
exceedingly expensive, which limits the type of study in which they are useful, and
as with the ‘sound’ detectors, placing of the transducer is critical. Minor shifts can
lead to gross artefact. Another disturbing feature is the production of ‘hard’ copy.
A systematic error in the equipment can be perpetuated and produce readings which
look acceptable but may be grossly in error (34).

Infrasound is another echo-sounding technique used to detect wall movement, but
this technique has been shown to be inaccurate and misleading (36).

V. MULTIPLE MEASUREMENTS

Physicians have long been aware of the drawbacks inherent in the Riva-Rocci/Ko-
rotkov technique and the possibility of inaccurate recordings leading to wrong deci-
sions. The clinician is more interested in the prognostic power of a reading than in
its precision, but the indirect technique is so imprecise that it hardly inspires confidence. This was clearly illustrated by the work of Goldberg (37) who showed that clinic readings of blood pressure in treated hypertensive patients could be grossly misleading and might lead to increasing dosage of antihypertensive drugs to levels which could be dangerous. He also drew attention to the fact that conclusions about the efficacy of antihypertensive therapy drawn from clinical trials using the indirect method could be very misleading.

Repeated measurements would logically seem to be more likely to provide a representative value of blood pressure and have a powerful appeal for the practising physician. Most authorities recommend that readings should be repeated at regular intervals on at least 3 occasions before any decisions are taken, despite the lack of evidence that such a mean level contains any more (or less) prognostic information than a single casual reading.

If multiple recordings are likely to improve precision and give more useful clinical information, then it is only logical to train patients to record their own blood pressure using the indirect technique and thereby obtain the required number of readings. This approach has been attempted by a number of physicians, but an alternative and more popular technique is the use of automatic and semi-automatic devices to do the work (38).

The number of these machines which are commercially available is increasing at an almost epidemic rate, because the technology is cheap and readily available and public awareness of the significance of high blood pressure has been heightened by publicity campaigns. Many of these instruments offer both the oscillometric and the auscultatory techniques for measuring blood pressure, but few have been properly validated, and it is unlikely that they will have any enhanced accuracy over self-measurement because they operate on exactly the same principles (39). It cannot be emphasized enough that no new principles for the indirect measurement of blood pressure have been introduced by these machines.

The emphasis in blood pressure measurement has been shifted by recent large-scale trials, from casual office observations of high readings which clearly demand treatment to close observation of borderline readings for which the therapeutic benefit of treatment is small unless those subjects at greater risk of cardiovascular pathology can be identified. In other words, cost/benefit ratios have been sharply focused. It is in the area of moderate elevation of blood pressure that the need for accuracy is paramount. The indirect techniques are open to doubt and question. The direct techniques are accurate beyond question, but are too invasive for general usage. The stage is open for new and innovative techniques of indirect measurement. Alas! There appear to be few takers.

REFERENCES


3. Sphygmomanometers in clinical practice and research

G. Fowler, M.J. Jamieson, D. Lyons, T.A. Jeffers, J. Webster and J.C. Petrie

The aim of the chapter is to discuss the use of blood pressure measurement in clinical practice and research of mercury column, aneroid, London School of Hygiene, Hawsley random-zero sphygmomanometers and semi-automatic devices.

The principal points which require to be highlighted in the training of observers have been summarized in a booklet *The Measurement of Blood Pressure* prepared by a Working Party of the British Hypertension Society (BHS) (1, 2). A 30-minute BHS training video accompanies the booklet (3). Failure to follow a standardized methodology leads to erroneous blood pressure measurement which leads to inappropriate management decisions. This chapter assumes familiarity with the points which are highlighted in the booklet and film.

1. MERCURY COLUMN AND ANEROID SPHYGMOMANOMETERS

The mercury column sphygmomanometer remains the standard for routine use in clinical practice if it is properly maintained. It is not presently favored for clinical research where ‘blinding’ of observers is preferred.

Aneroid sphygmomanometers are an alternative to mercury column sphygmomanometers for routine service use. They are preferred by some practitioners because they are portable. Aneroid sphygmomanometers must be particularly well maintained because they tend to lose accuracy over a period of months and require frequent re-calibration, 6- or 12-monthly.

Despite the emphasis which has been repeatedly placed on the appropriate training of observers and the regular maintenance of mercury and aneroid instruments the use of defective equipment and inappropriately sized cuffs to measure blood pressure remains commonplace. The principal problems which have been reported with mercury column and aneroid machines include poor visibility of the mercury meniscus in the mercury manometer, faulty calibration of the mercury column and illegibility of the scale. The inflation/deflation devices frequently malfunction due to faulty control valves, blocked air vents and/or filters, and/or perished tubing.
Numerous studies have reported these continuing problems over the years and make depressing reading.

For example, Conceição and co-workers found that half of the sphygmomanometers in a teaching hospital had faults in the control valve which interfered with accurate blood pressure reading. The cuffs used did not encircle the arms of more than half of the patients upon whom they were placed (4).

Faults in the inflation–deflation system were common (5). They are caused mainly by dirt or wear in the control valves. Leakage occurred in 48% of the hospital and 33% of the family practice sphygmomanometers studied (5). In mercury models the mercury air vents are often in an unsatisfactory condition or the calibrated glass tube is dirty. Thirty percent of the aneroid sphygmomanometers (compared with less than 2% of the mercury column sphygmomanometers) have errors greater than ± 4 mmHg.

Fisher studied the accuracy of 3390 aneroid sphygmomanometers which were calibrated against mercury sphygmomanometers during routine servicing (6). Differences between the aneroid and the mercury column sphygmomanometer exceeding ± 3 mmHg were noted in 22% of the aneroid instruments at 60 mmHg, in 25% at 120 mmHg, in 29% at 180 mmHg, and in 34% at 240 mmHg.

Similar findings have been reported by Bowman (7). All the aneroid sphygmomanometers in use on acute medical and surgical wards of a major teaching hospital were examined. On at least one test pressure, 11 out of 13 hand-held instruments under-read by 5 mmHg or more compared with the pressure reading of the mercury sphygmomanometer. Six of these deviated by at least 10 mmHg and two by 20 mmHg. Of the 10 wall-mounted aneroid sphygmomanometers tested 5 under-read by at least 5 mmHg.

Such reports emphasize the importance of the BHS recommendations (1, 2) that a defined maintenance and servicing policy, and a person responsible for the policy, are required for each clinical area where mercury column and aneroid systems are used to measure blood pressure.

The London School of Hygiene sphygmomanometer

The London School of Hygiene (LSH) instrument was developed almost 30 years ago in an attempt to eliminate observer bias in clinical research and in epidemiological studies (8, 9). Digit preference and observer bias are reduced by the LSH device since the blood pressure can only be determined by the observer upon completion of the measurement because the manometer is concealed from the observer. The LSH device is still used occasionally but has been largely superseded by the more convenient Hawksley random-zero instrument.

The LSH sphygmomanometer slightly underestimates blood pressure (10). The method of activating the recording (see below) leads to the observer tending to delay pressing the plunger valve until he is certain that he has heard the first Korotkov sound. Similarly, the diastolic pressure is actioned when an expected Korotkov sound fails to occur (Phase V). Calibration errors have also been reported (10, 11).

The LSH sphygmomanometer has other minor disadvantages. It weighs 11.4 kg. It measures 25 × 26 × 51 cm. Because of the technique used, measurements take longer to perform than with mercury column or aneroid sphygmomanometers.
The LSH sphygmomanometer is an ingenious device. It consists of 3 concealed mercury manometers situated side by side within the cabinet. Each manometer is connected to a plunger valve mounted on the front of the cabinet. A fourth plunger valve controls cuff inflation. A tunnel in the base of the block connects with the base on each manometer and also with tubes leading to the rest of the circuit. When one of the plunger valves is depressed, the piston switches the manometer out of the circuit. Within the cabinet a 0.4 kg cylinder of carbon dioxide provides a pressure source which inflates the cuff to a pressure of 280 mmHg. Cuff deflation is initiated by closing the valve. By turning a handle on the side of the cabinet a cursor is lowered to the level of the top of the mercury meniscus on the concealed manometer. A flap above the manometer is then opened and the recorded blood pressure value is obtained to the nearest mmHg.

*Fig. 1.* The Hawksley random-zero instrument. Note that the random zero has settled at 88 mmHg (manometer scale), with the diaphragm tap (front left of scale at 'open'). The wheel (rubber rim) which is spun to vary the random zero is clearly visible to the right of the mercury reservoir.
The Hawksley Random Zero sphygmomanometer

The Hawksley Random Zero sphygmomanometer (HRZS) (Fig. 1) was developed for use in research studies to overcome the limitations of the LSH machine (12). It is based on the ‘zero muddler’ sphygmomanometer (14, 15).

The HRZS is regarded as the most appropriate device for occasional blood pressure measurement in a clinical research setting such as in the evaluation of the efficacy of drugs and in epidemiological studies. Despite the portability of the HRZS and the visible falling mercury column it has not, and apparently will not, displace the mercury column or aneroid sphygmomanometer in routine clinical practice.

The Hawksley device has consistently been shown to underestimate both systolic and diastolic pressures. For example, Evans and Prior (15) found mean differences of −1.2 mmHg (systolic) and −2.2 mmHg (Phase IV diastolic) in 906 subjects. Labarthe and colleagues (16) found mean differences of −1.6 (systolic), −2.6 (Phase IV) and 2.7 (Phase V diastolic) mmHg in making multiple measurements in 24 subjects. de Guademaris and co-workers (17) found differences ranging from −0.77 to −3.06 mmHg systolic and −1.04 to −2.36 mmHg Phase V diastolic in a series of 6 protocols each of 40–500 recordings. Finally, Parker and colleagues (18) found mean differences ranging from −2.5 to 3.3 mmHg systolic and −1.9 to −2.7 mmHg (Phase V diastolic) making simultaneous single-arm comparisons.

The HRZS device, by design, reduces observer bias and disguises digit preference. Nevertheless the HRZS does not eliminate bias. There is no difference between the Hawksley and the mercury sphygmomanometer in the distributions of terminal digits, nor are the random-zero values distributed in truly random fashion (17, 18). However, from a practical point of view the zero values are sufficiently unpredictable, provided the instrument is used correctly (see below), to minimize preconceptional bias.

A practical problem in using the HRZS is that in patients with high systolic pressures above 240 mmHg measurement difficulties are encountered because the reading on the manometer incorporates the ‘hidden’ random-zero component (which may vary from 0 to 60 mmHg). Thus inflation of the cuff to 30 mmHg above the anticipated blood pressure (including the variable 0–60 mmHg component of the random zero) is not possible since the manometer only reads to 300 mmHg.

In respect of care and maintenance the HRZS instrument requires more maintenance than the simpler mercury column and aneroid devices because of its more sophisticated features. The control-release valve diaphragm may perish or be perforated by overenthusiastic tightening. Ingress of air and loss of mercury occur. The virtually constant presence of mercury in the first 0–80 mm of the column increases the tendency to mercuric oxide deposition which interferes with accurate reading of the random-zero value.

The HRZS is a sophisticated successor to the LSH device. For the observer to become proficient in operating the HRZS it is useful to observe its actions with the casing removed. This allows the observer to understand the interrelationships of the thumb wheel/cam position, the volume of the diaphragm chamber and the ‘zero’
value, and to appreciate the considerable time taken (up to 5 seconds) for the diaphragm chamber to fill with mercury.

With the casing removed the HRZS comprises a standard 300-mm mercury column manometer connected to a 60-ml mercury reservoir which communicates via a diaphragm tap to a diaphragm chamber. The chamber is ordinarily held empty by the action of a spring against the diaphragm. When the sphygmanometer cuff is inflated, the pressure rises in the reservoir and mercury enters the manometer. The mercury is also expelled into the diaphragm chamber, pushing the diaphragm out against the spring. Maximum excursion of the diaphragm assembly is limited by its abutment against a spiral-faced cam. The volume of the diaphragm chamber, and therefore the residual volume of the reservoir, is determined at any time by the position of the spiral cam. This position can be varied in a random fashion by means of a thumb wheel which is spun by the observer prior to each measurement. The residual volume of the reservoir when the pressure is released determines the 'random zero' position of mercury in the manometer. The diaphragm chamber and the cam, within the overall casing, are normally invisible to the observer.

Once the principles underlying the design of the HRZS are understood, operating the instrument is relatively straightforward but must be done correctly. The diaphragm tap is set to ‘open’. The meniscus of the mercury in an adequately filled instrument settles at about 80 mmHg (40 mmHg in the North American version). The cuff is then inflated to above 240 mmHg and maintained at that level for about 5 seconds to allow the diaphragm chamber to fill properly. This normally takes about 5 seconds at 240 mmHg. Failure to allow this interval restricts the range of zero values. The diaphragm tap is then switched to ‘close’. The mercury column is then allowed to fall under control of the device’s constant-release valve. After the systolic and diastolic blood pressures have been recorded by the observer, any remaining pressure is released. Once the system has come into equilibrium the ‘random zero’ reading, which will lie between 0 and 60 mmHg, is read from the mercury meniscus. This figure is then subtracted from the systolic and diastolic recordings. Arithmetic errors by observers occur in the subtraction process and the original readings, together with the ‘random subtraction’ figure, should always be recorded as source data to avoid this problem.

II. SEMI-AUTOMATIC DEVICES

Portable instruments which would minimize the problems of observer error and permit repeated automatic or semi-automatic accurate, reliable, repeated indirect measurement of blood pressure would be of immense benefit to clinicians, researchers and patients. Such instruments would have considerable advantages over single readings obtained with mercury column, aneroid, LSH or HRZ sphygmomanometers. Such automatic instruments, before they could be recommended for use, would of course require to be proven in respect of accuracy, reliability, convenience, robustness, lack of inter-device variability, and security of servicing back-up. Few of the studies reported to date provide convincing supportive evidence that such criteria have been fulfilled.
The first device based upon the auscultatory principle was developed in 1962 (19). Since then numerous automatic sphygmomanometers have been produced which rely on either auscultatory, oscillometric, Doppler ultrasound or plethysmographic methods. Unfortunately there has been no obligation to provide evidence regarding the accuracy and reliability of such instruments. This state of affairs has attracted adverse comment because devices have been promoted and sold for a period of time before independent validation studies have been carried out (20).

The publication of standards and protocols against which to validate the devices should go some way to reduce these problems for users and purchasers of devices in the future. Of course the setting of standards to be met has complicated the development of instruments from the manufacturer’s point of view! Foremost amongst the standards/guidelines has been the Association for the Advancement of Medical Instrumentation (AAMI) guidelines for semi-automatic and automatic devices (21). The BHS Working Party has also recently published a recommended protocol (22). This detailed protocol develops the AAMI guidelines and addresses additional factors such as inter-device variability, and ambulatory assessment.

The BHS protocol suggests that a Grade B category is appropriate when more than 65% of readings agree within 5 mmHg of each other; or if more than 85% agree within 10 mmHg; or more than 95% agree within 15 mmHg of each other. Devices which appear on the market over the next few years require to be judged, according to the BHS recommendations, using these criteria.

The adequacy of validation studies on sphygmomanometers carried out prior to publication of the newer guidelines requires to be carefully re-assessed. It is apparent that many of the studies reported have deficiencies. Some are too small and/or report correlation and regression analyses which are not now considered to be appropriate for assessing agreement between two methods of clinical measurement (23).

Devices based on the auscultatory method

Since the conventional means of indirect blood pressure measurement relies upon the auscultatory method, it is logical that this method should have been the first to be adapted for automatic blood pressure measurement.

The Remler M2000 automatic blood pressure recorder

In 1962 Hinman and colleagues (19) developed a portable semi-automatic blood pressure recorder as a means of obtaining new information on diurnal blood pressure variation. The apparatus comprised a mercury column, blood pressure cuff with bulb, a button microphone, a frequency-modulated pressure transducer and a tape recorder. Cuff inflation was initiated by the subject. Controlled deflation occurred automatically. The pressure in the cuff and the Korotkov sounds detected by the microphone were recorded onto tape. Upon completion of a set of recordings, the tape was decoded through a system calibrated with a mercury manometer. This produced a pen-recording upon which the Korotkov sounds appeared as deflections of the pen. The device can record pressures up to 250 mmHg. This apparatus was modified and marketed as the Remler M2000 automatic blood pressure recorder.
The Remler has been validated by several groups. Fitzgerald and co-workers (10, 24) assessed the accuracy and reliability of the Remler M2000 and Cardiodyne Sphygmolog blood pressure recorders. The three Remler devices were in agreement but one Sphygmolog device persistently recorded higher. No difference was found between simultaneous measurements with the Remler and the Hawksley Random Zero sphygmomanometer in 58 patients. The reliability of the Remler was assessed from 69 attempted day recordings. Five day recordings failed due to a defective microphone lead. Of the 64 successful day recordings 9.2% of blood pressure data could not be decoded. A further 3.1% failed due to the microphone not detecting the Korotkov sounds.

The accuracy of the Remler against the mercury sphygmomanometer was assessed in 12 normotensive volunteers by Brunner and colleagues (25). The mean difference between the Remler and the standard sphygmomanometer for systolic and diastolic pressure was approximately −4 and 4 mmHg. The authors concluded that the Remler M2000 semi-automatic blood pressure recorder provided reliable blood pressure profiles in the ambulatory subject.

Gould and colleagues have (26) compared the Remler M2000 with intra-arterial and Hawksley blood pressure readings in 28 patients with a wide range of blood pressures. Ten percent of readings could not be analyzed due mainly to arm movement and equipment failure. When the Remler was compared with intra-arterial blood pressure readings, the mean difference was −3 mmHg (systolic) and 7 mmHg (Phase V diastolic). However, when the Remler was compared with the Hawksley, the differences were smaller, being 3 mmHg (systolic) and −2 mmHg (Phase V diastolic). The authors concluded that the Remler M2000 automatic blood pressure recorder agreed reasonably well with clinic pressures although large differences were occasionally seen.

Jacot des Combes and co-workers (27) used the equipment to study whether clinic blood pressure measurements are representative of those recorded in the ambulatory setting. Two observers obtained a total of 2000 ambulatory blood pressure measurements in 101 subjects with a wide blood pressure range. Only 3−4% of readings were unsuitable for analysis. The authors concluded that the Remler M2000 blood pressure recorder, when used properly, provides a reproducible blood pressure profile during daily activities.

These different studies confirmed that the Remler M2000 portable blood pressure recorder is reasonably accurate in the measurement of blood pressure. Arm movement during exercise reduced its performance. The minor difficulties referred to above, together with its bulkiness, slightly labor-intensive decoding function, and high cost were among the disadvantages of this otherwise very satisfactory machine. It has now been largely superseded by more sophisticated devices.

*The Copal UA-231 and UA-251 semi-automatic sphygmomanometers*

The Copal UA-231 and the Copal UA-251 semi-automatic sphygmomanometers represented a considerable advance when they were first introduced a decade ago by the Japanese company, Takeda Medical. The two devices function similarly. The Copal UA-251 has a printing facility.
Both devices employ the auscultatory method and are compact and convenient to use (Fig. 2). They are either mains- or battery-operated. The dimensions are $17 \times 26 \times 7$ cm. The weight is 1200 g. Only one cuff size is provided. The cuff (bladder $12 \times 22$ cm) is smaller than that now recommended (35 cm) by the BHS for routine use (1, 2). The Velcro fastening cuff contains a microphone which is positioned by the operator or patient over the brachial artery 5 cm above the antecubital fossa.

The cuff is inflated to a pre-set limit automatically by pressing a ‘start’ button. Cuff deflation (rate $2-7$ mmHg/s) proceeds automatically. Phase I and V Korotkow sounds are detected and a visible and an acoustic signal is emitted at each beat. The pulse rate is estimated from the first 5 beats after the measurement of systolic pressure. After measurement of diastolic pressure the cuff deflates rapidly. The reading is shown on a liquid crystal display. The pressure measurement range is $20-280$ mmHg. The measurement cycle time is 40 seconds.

The UA-231 has been evaluated by several groups. It has been compared with the Hawksley Random Zero sphygmomanometer (HRZS) in volunteers with a wide range of blood pressure (28). The Copal UA-231 provided a comparable estimation of diastolic pressure, but there was a systematic difference of 5 mmHg in systolic blood pressure. The Copal UA-231 has also been assessed for suitability for use in epidemiological surveys (29) and the mean difference between the Copal UA-231 and the Hawksley Random Zero devices was $+2.3$ mmHg for systolic and $+1.9$ mmHg for Phase V diastolic pressure. The Copal UA-231 error increased with higher mean blood pressure. A 10 mmHg increase in mean diastolic blood pressure was matched with a 1.15 mmHg increase in the diastolic difference. The authors
concluded that the Copal UA-231 is a useful instrument for epidemiological survey work since it is lightweight, compact, easy to use, and removes some error in the measurement of blood pressure.

The Copal UA-231 has been adapted to the ambulatory setting by securing the cuff with adhesive tape to the upper arm and placing the monitor in a shoulder bag (30). Conway and colleagues suggest that the Copal UA-231 is accurate.

The Copal UA-251 versus the Hawksley Random Zero sphygmomanometer (HRZS) In the first of these studies Malatino and Brown studied sets of duplicate blood pressures measurements performed simultaneously in 68 patients (31). The mean difference between the Copal UA-251 and the HRZS was −0.45 mmHg and −0.95 mmHg for systolic and diastolic pressure respectively. No systematic variation was apparent over the blood pressure range measured in contrast with Gallacher and colleagues’ findings (28). During the evaluation only one measurement failed. Malatino and Brown concluded that the Copal UA-251 was technically efficient, showed good comparison with the HRZS and was useful in the clinical setting. The inability to alter cuff size was a disadvantage.

Steptoe and Molineux (32) assessed the reliability and accuracy of the Copal UA-251 under conditions of rest and exercise. The Copal UA-251 had a higher failure rate than was noted by Malatino and Brown. Failed readings were due to air leak (n = 4), movement (n = 4), pressure setting too low (n = 2) and battery failure (n = 1). The Copal UA-251 was reported to record systolic blood pressure 2.3 mmHg higher than the HRZS but measured resting diastolic blood pressure adequately. The overestimation of systolic blood pressure was thought to be due to the microphone being more sensitive than the observer, a comment also made by Maheswari and colleagues (33). Steptoe and Molineux recommended the Copal UA-251 as a suitable instrument for the self-recording of blood pressure.

Crombie and co-workers (34) assessed the performance of the Copal UA-251 in 1464 subjects. Twelve trained observers performed two pairs of measurements with the HRZS followed by a third pair with one of two Copal UA-251 devices. The range of differences for the 12 observers was −7.7 to +3.0 mmHg for systolic blood pressure and −6.6 + 4.1 mmHg for diastolic blood pressure, The Copal UA-251 overestimated blood pressure by 0.58 mmHg for systolic and 1.93 mmHg for diastolic blood pressure. When comparing the average HRZS-measured blood pressure with the Copal UA-251, reading discrepancies were seldom seen for systolic blood pressure. Sixty-eight of 2928 diastolic blood pressure readings differed by over 30%. One Copal UA-251 device recorded some diastolic pressures considerably higher than the other. Inter-device checking prior to the study would have avoided this problem. This is an important point which is highlighted in the BHS recommendations (22). Crombie and colleagues concluded that the Copal UA-251 sphygmomanometer performs to a high standard. They recommended that high diastolic blood pressure readings which appear to be spuriously high should be repeated.

In an assessment carried out by Lindsay and colleagues (35) triplicate blood pressure were recorded sequentially with the Copal UA-251 and HRZS in 93 patients. In a further 19 patients simultaneous blood pressures were recorded on opposite arms. Twelve more patients had simultaneous Copal UA-251 and intra-
arterial measurements performed. In those patients who had sequential blood pressure recordings, the mean pressure recorded with the Copal UA-251 and HRZS sphygmomanometers were 134 and 129 mmHg respectively for systolic blood pressure and 80 mmHg for both devices for diastolic blood pressure. The results for blood pressures recorded simultaneously were 122.5 and 119 mmHg for systolic and 74.5 and 73.6 mmHg for diastolic with the Copal UA-251 and HRZS respectively. The authors concluded that the Copal UA-251 device was suitable for screening programs and home blood pressure monitoring.

Maheswaraen et al (33) compared the Copal UA-251 device with the HRZS in 53 subjects. Two trained observers, using a double-headed stethoscope, performed simultaneous measurements with the Hawksley and test device attached to opposite arms. Cuffs and machines were then swapped to opposite arms and a second measurement recorded. The Copal UA-251 recorded higher systolic blood pressure than the HRZS in 74% cases (mean differences 4.6 mmHg). This discrepancy widened at the higher end of the blood pressure range. The agreement between machines was reasonable for diastolic blood pressure (mean difference −0.5 mmHg). They concluded that the Copal UA-251 is suitable for home blood pressure monitoring. They suggested that the piezo-electric microphone is more sensitive than the human ear in its ability to pick up Korotkov sounds at an early stage.

*The Copal UA-251 versus other semi-automatic devices, and intra-arterial pressure recording*  Maheswaraen and colleagues (33) compared both the Copal UA-251 and the Dinamap 1848 oscillometric device with the HRZS using the methods outlined above. The Dinamap was used in 56 subjects. The agreement between machines was reasonable for diastolic blood pressure, the mean difference being −0.5 mmHg.

Johnson and Kerr (36) compared intra-arterial pressures against the Copal UA-251 and Vitastat devices (auscultatory method) and against more sophisticated and expensive oscillometric devices such as the Dinamap 845XT, Nacro, and Sentron (Bard). Blood pressures obtained with the semi-automatic devices were compared with intra-arterial pressures recorded immediately prior to inflation of the cuff which was placed on the same arm in 48 patients in an intensive care unit or undergoing neurosurgery. The blood pressure range studied was therefore necessarily limited. Recordings were made every 5 minutes and up to 41 measurements were recorded per patient. Several anesthetists obtained data with the Sentron device, whilst one or two observers acquired data with the other devices. Readings obtained with the Copal UA-251 and Sentron devices were closer to radial artery measurements than were those obtained with the other devices. None of the devices was consistently able to record systolic blood pressures below 60 mmHg. Faults developed with 3 monitors: the inflation pump in the Sentron became loose; a washer at the cuff-hose junction failed in the Dinamap resulting in underestimation of blood pressure; the Vitastat occasionally displayed a mean arterial pressure which exceeded the systolic pressure, indicating a microprocessor programming error. No faults were observed with the Copal or Narco devices. Overall Johnson and Kerr considered the Sentron to be the best of the devices tested. They pointed out that at a tenth of the price the Copal UA-251 proved to be as accurate as the Sentron and ought to be considered as a method of monitoring anesthetized patients.
Evaluations of other auscultatory devices

In a small study Rubin and colleagues compared the HRZS, Bosomat 11D, Elag Kohn BE 237R and Omron HEM 3 in 18 subjects (37). The devices did not differ significantly from each other, or from the HRZS.

Sloan and colleagues studied 4 semi-automatic devices which employed the auscultatory principle and compared them with the HRZS (38). The Astropulse II showed marked deviation in average blood pressure recorded and greater variation in readings. The Infrasonde M3010, Bosomat II and Infrasonde D4000 were similar to the HRZS.

The Pollenex BP-850 automatic sphygmomanometer contains the same circuitry as the Copal UA-251. The device was evaluated by Bennett and co-workers (39) in 120 volunteers who were divided into 3 groups of 40. In the first group the HRZS and Pollenex were compared with each other. In this situation the mean differences were 0.6 mmHg (systolic) and 1.42 mmHg (diastolic). A wider discrepancy was found when the HRZS was compared with a silenced Pollenex. The acoustic signal produced by the standard Pollenex influenced the observer. The silenced Pollenex recorded consistently, though not significantly, higher readings than the HRZS. The workers suggested applying limits of acceptable performance as two standard deviations ± 2 mmHg for clinical research, and ± 5 mmHg for clinical practice. Using these self-imposed arbitrary criteria and using the methods employed in this study, both the Pollenex BP 850 and the HRZS failed to provide a reliable measurement of blood pressure!

Automatic blood pressure devices are frequently used in intensive care units. The IVAC Vital-Check blood pressure monitor contains a microphone in the pressure cuff which detects the Korotkov sounds (Phase I and V). It also incorporates a facility for recording an oscillometric measurement of systolic pressure. This device has been evaluated in the intensive care setting (40, 41).

Davis compared the systolic, diastolic and mean arterial blood pressure measurements obtained with the auscultatory mode with intra-arterial pressure in 50 patients undergoing surgical procedures. In a subset of 12 patients recordings were compared with manual auscultatory and intra-arterial measurements (40). There was close correlation between the oscillometric and intra-arterial measurements (mean differences 5.2 ± 0.4 mmHg for systolic blood pressure, 3.7 ± 0.5 mmHg for diastolic blood pressure and 2.3 ± 0.4 mmHg for mean pressures). Agreement between the 3 techniques was found in the subset who had additional manual auscultatory readings performed (mean intra-arterial BP 117/66 mmHg, mean oscillometric BP 111/64 mmHg, mean auscultatory BP 111/71 mmHg and mean manual auscultatory BP 110/73 mmHg). Davis (40) concluded that the IVAC Vital-Check monitor met the AAMI validation guidelines (21). Both the auscultatory and oscillometric modes tended to underestimate systolic and overestimate diastolic blood pressures.

Rebensen-Piano and colleagues studied the device in 32 patients from the intensive care unit and compared it with intra-arterial (radial artery) measurements and the mercury column sphygmomanometer (41). The sequence of Vital-Check and standard sphygmomanometer measurements was randomized to eliminate any order effect. Both indirect methods of blood pressure measurement underestimated
systolic blood pressure. The difference was significant only between the direct method and the Vital-Check monitor. In normotensive patients the Vital-Check monitor and the direct method produced almost identical values for diastolic blood pressure. The mean value obtained with the mercury column sphygmomanometer was higher. The authors concluded that the Vital-Check microphone is more sensitive and consistent than the observer in determining Korotkrov sounds. They recommended the IVAC Vital-Check automatic monitor as an adequate substitute for the standard sphygmomanometer in patients without hypotension in the intensive care setting.

Most of the auscultatory methods of automatic blood pressure measurement display the readings in digital format. They do not allow authentication of the Korotkrov sounds. The Khi Objective blood pressure measurement system OHM-V3 was developed by Fukuoka and colleagues (42). This device produces a digital display of the arterial pressure pulse wave and the Korotkrov sounds detected during blood pressure measurement. The technique relies upon the evaluation of the changes in signal pattern rather than in amplitude of Korotkov sounds. A microcomputer is used to analyze the events detected by the microphone as systolic and diastolic pressure values. A pen-recording of arterial pressure and microphone signal is obtained during cuff deflation. The Khi device automatically displays systolic and diastolic values. Readings are also obtained directly from the pen-recording. As the cuff pressure falls, the signal detected by the microphone changes from a simple waveform to a more complicated shape that initially increases in amplitude and then decays. The 5 blood pressure phases and the relationship between the microphone signal and the arterial pressure wave are identified.

Fukuoka and colleagues (42) studied the accuracy of the device by comparing it with simultaneous intra-arterial (brachial artery) pressure measurements. Measurements were performed on 29 patients undergoing brachial artery catheterization during investigation of cardiac disease or hypertension. The cuff and intra-arterial values showed a close correlation for systolic and diastolic blood pressures. The difference between the indirect and direct readings ranged from −14 to +9 mmHg for systolic blood pressures and from −5 to +14 mmHg for diastolic blood pressure. They comment that the Khi device produces blood pressure values which correspond well with concurrent intra-arterial pressure values.

The Hitachi HME-20 digital blood pressure monitor has been evaluated by Ho and colleagues (43) against the standard mercury sphygmomanometer as the reference instrument. Simultaneous blood pressures were recorded with the Hitachi HME-20 monitor on the left arm and the standard sphygmomanometer attached to the right arm. Duplicate blood pressure measurements were performed in 54 students. The HME-20 consistently underestimated blood pressure, particularly diastolic pressures. They concluded that the HME-20 tends to underestimate systolic and diastolic pressures and suggested that it is more suitable for following trends in blood pressure rather than in the accurate determination of single blood pressure readings.

**Devices that employ the oscillometric method**

Oscillometry, a method for the measurement of blood pressure initially developed almost 100 years ago (44), has been employed in a range of automated devices which
have been introduced since the mid-seventies (45). The general principle employed is that pulsatile blood flow produces oscillations of the blood vessel that are transmitted to the cuff. The sudden increase in pulse pressure that accompanies pulse breakthrough may lead to an overestimate of systolic blood pressure by such devices when auscultation is used as the comparator.

*Dinamap (Critikon)*

The Dinamap is one of the principal devices on the market. Dinamap is an acronym for ‘Device for Indirect Non-invasive Automatic Mean Arterial Pressure’. With the cuff positioned over the artery the proximal bladder is inflated to occlude blood flow while residual air volume is maintained in the distal bladder. The proximal bladder is then automatically deflated in a stepwise fashion until restoration of blood flow causes arterial wall oscillations that are detected in the distal bladder. The cuff is inflated and deflated through a double hose system. There is an artefact rejection program which identifies two consecutive matched pulses at each pressure step so that extraneous noise can be rejected.

Numerous evaluations of the different Dinamap devices have been carried out since the prototype versions were reported in 1979 (45). As with the evaluations on auscultatory devices many of these reports, with some important exceptions, have flaws in their design, conduct, statistical power, and range of blood pressures studied. Not surprisingly, few of the older studies have used presently preferred statistical methods and have relied on the presentation of what are now considered to be inappropriate correlation coefficients and regression analysis (23). The result is that conflicting reports have appeared. Some of these are summarized below. Mean differences in large numbers of comparison measurements of the Dinamap against other reference systems have been small (less than 5 mmHg). However, standard deviations of mean differences in blood pressure determinations, which reflect the presently recommended statistical analysis using limits of agreement, have been inconsistently within acceptable limits.

New models have been introduced as the models are enhanced. For example, the Dinamap 845, Dinamap 1846 and 1846P (with printing unit) adult/pediatric models, Dinamap 847 neonatal monitor (46) have now been replaced by newer versions.

Of the presently available models the Dinamap 1848 weighs 9.6 kg and is dependent upon a mains power supply. There is a digital display and a built-in printer. The Dinamap 1846SX has a pressurized reservoir pump system which effects very rapid cuff inflation. It is claimed to cause less discomfort to the patient. The SXP has a printer. A built-in pulse oximeter to provide oxygen saturation values is an additional feature on the 1846SXP ‘Oxytrack’ version. The Dinamap 8100 is a programmable portable version which is mains-electricity- or battery-operated. The 8100T has a feature to display temperature.

*Dinamap versus the Hawksley Random Zero Sphygmomanometer (HRZS)* Silas and colleagues assessed the Dinamap 845 against the HRZS in 32 adults over a wide range of pressures (47). The mean diastolic blood pressures (Phase IV) recorded by the device were 3.4 mmHg lower. The systolic readings were almost identical. Standard deviations for differences between devices were not reported. The authors
criticised this model because of an upper maximum limit of recording of 210 mmHg.

Maheswari and co-workers reported that the Dinamap 1848 consistently overestimated systolic blood pressure at pressures up to 145 mmHg, the median difference being 7 mmHg (33). Beyond this level the difference was less obvious. The Dinamap tended to slightly underestimate diastolic blood pressure, the median difference being 2.5 mmHg.

Ornstein and colleagues evaluated the portable Dinamap 8100 device against the HRZS in 80 normotensive and hypertensive ambulatory patients using a factorial design (48). They found that the device overestimated systolic readings (mean difference 7.6, SD 9.1 mmHg) and more than one-third of systolic measurements and one-quarter of diastolic measurements were greater than 10 mmHg discrepant from the standard. The authors concluded that the device did not meet acceptable standards of performance. Routine use of the Dinamap 8100 would lead to serious misclassification errors in screening for hypertension and in the follow-up of hypertensive patients. They cautioned that the Dinamap 8100 is not an appropriate instrument for routine use in primary-care settings.

_Dinamap versus mercury column and/or LSH sphygmomanometers_ Waikakui and Prakantrattana compared the Dinamap 845XT with conventional sphygmomanometry measurements in 75 patients undergoing cardiac surgery in non-randomized order (49). The Dinamap showed systolic blood pressure 12 mmHg higher and diastolic blood pressure 3.51 mmHg lower than conventional sphygmomanometry.

Ellison and colleagues studied 35 subjects using a computer-linked Dinamap 845A – sphygmomanometer system (50). Scatter plot differences of 5 and 10 mmHg were not uncommon.

The Dinamap 845 and Sentry were evaluated in 30 hypertensive patients using triplicate measurements by Bassein and colleagues (51). The devices were tested in random order. There was a clear lack of reproducibility. The mean diastolic blood pressure readings were considerably lower with both machines (about 7 mmHg) than standard mercury column measurements and by at least 10 mmHg in 25% of measurements. Agreement was better for systolic pressure. The authors cautioned that classification of patients as normotensive may depend on the device used.

Milsom and colleagues compared the Dinamap (model not stated), intra-arterial pressure and manual sphygmomanometry in only 10 healthy women in the last trimester of pregnancy and claimed close correlations between all 3 methods (52).

Lindé and Wright found no statistically significant differences in blood pressure recordings in only 15 subjects using standard sphygmomanometry and the Dinamap 845 (53). Nevertheless the mean Dinamap diastolic blood pressure reading was 5.2 mmHg lower. Standard deviations were not reported and the study may have been subject, along with similar small studies of this type, to a type 2 statistical error.

Park and Méndez assessed the Dinamap 1846, conventional sphygmomanometry, and direct radial artery pressure in children (54). Inspection of the data shows that the error for auscultatory versus direct pressures ranged from −14 to +19 for systolic and −2 to +22 mmHg for diastolic blood pressure.
Jenner and co-workers evaluated the Dinamap 845XT against the LSH and conventional mercury device in 31 normotensive and hypertensive subjects (55). Twelve sets of readings were obtained with each device in each subject. Differences between the single Dinamap unit tested and standard mercury averaged across all subjects were small. Inter-device differences were small. Nevertheless differences between measurements taken simultaneously were often substantial. Agreement between the two mercury sphygmomanometers was better than that between either sphygmomanometer and the Dinamap. The authors cautioned against interchangeable use of Dinamap instruments and mercury column measurements. They also warned against translating the results to another 845XT unit other than the Dinamap 845XT device that they tested, or to other Dinamap instruments such as the 1846. The BHS guidelines reinforce this point (22).

The Dinamap versus intra-arterial pressure In an early study the Dinamap device (model not specified) was evaluated by Venus and colleagues in a critical care center in 43 patients (56). The authors concluded that the Dinamap underestimated systolic blood pressure by a mean of 9.2 (SD 16.4) mmHg and overestimated diastolic blood pressure by a mean of 8.7 (SD 10.6) mmHg. Large errors occurred within individuals. They suggested that when accurate measurements are needed, indirect measurement may not be reliable.

Borow and Newburger evaluated 3 simultaneously obtained measurements obtained with the Dinamap 845 against central aortic pressure measurements in 30 patients undergoing cardiac catheterization (57). The authors assessed the reproducibility of the measurements for systolic pressure where the absolute difference was −11 to 13 mmHg and diastolic pressure when absolute difference was −7 to 11 mmHg.

Waikakui and Prakanrattana compared the Dinamap 845XT with direct intra-arterial measurements in 75 patients undergoing cardiac surgery in non-randomized order (49). The Dinamap showed systolic blood pressure similar to direct arterial pressure, but the diastolic pressure was 8 mmHg higher.

Hutton and colleagues assessed the accuracy of the Dinamap 845 against direct intra-arterial recordings (58) and concluded that in the majority of cases it was capable of producing trend information during anesthesia.

Loubser compared blood pressures measured with the Dinamap 1845 with direct radial intra-arterial recordings in 30 post-carotid-endarterectomy hypertensive patients (59). Mean differences of 18.92 and −6.32 mmHg were obtained for systolic and diastolic blood pressure respectively. Loubser suggested that mean differences in systolic blood pressure appeared to increase with increasing levels of blood pressure.

Adiseshiah and colleagues investigated the Dinamap (model not specified) for the measurement of ankle and brachial blood pressures (60). In 10 patients the difference in diastolic blood pressure (intra-arterial, Dinamap: −11.1 mmHg) was highly significant. The Dinamap under-read the systolic pressure by 20%, consistently across the range measured.

In the study by Park and Ménard mentioned above using the the Dinamap 1846, conventional sphygmomanometry and direct radial artery pressure in children, inspection of the data shows that the error for oscillometric versus direct pressures
ranged from $-7$ to $+7$ for systolic and $-9$ to $+10$ mmHg for diastolic blood pressure (54).

*The Dinamap versus systems using the Doppler principle* Adiseshiah and colleagues evaluated the Doppler and Dinamap for the measurement of ankle and brachial blood pressures (60). In 43 patients a correlation was found between systolic pressures between Doppler and Dinamap. A comparison was made with direct intra-arterial readings in a further 12 patients. The principal limitation reported was that the Dinamap did not record pressures below 50 mmHg.

*Devices using oscillometry*

The Sentron has been compared with intra-arterial measurements by Green and colleagues in 28 patients undergoing cardiac catheterization (61). The standard deviations of the observations obtained were wide. The correlations varied, apparently arbitrarily, with time. Systolic determinations correlated best.

The A & D (Takeda/Copal) UA-751, previously known as the Copal 751, is a semi-automated device which also employs the oscillometric principle. It weighs 650 g. The dimensions are $228 \times 132 \times 62$ mm (Fig. 3). Date, time, systolic and diastolic pressure and pulse rate are displayed on a liquid crystal display and can be stored in memory. There is a maximum capacity of 14 recordings. Operation is controlled by a single chip C-MOS microprocessor.

Inflation of the $12 \times 22$ cm bladder is to one of 4 pre-set pressures (160, 200, 240, 280, 320).
280 mmHg). The inflation is triggered by pressing a control button and driven by an internal pump. Deflation is governed by a constant exhaust valve throughout the recording period. Measurement in the range 20—250 mmHg is by pressure/capacitance manometer.

The device has been extensively validated. Winberg and colleagues compared the Takeda UA-751, the UA-251, conventional manometry and intra-arterial readings (62). Three indirect measurements were made in random order in the same arm in 40 subjects after 4—6 hours of the postoperative phase of coronary artery surgery. They also examined the individual variation of the difference between indirect and intra-arterial measurement. All 3 methods demonstrated a significant correlation with intra-arterial measurement. The intra-individual 'scatter' was smallest using ordinary auscultation. They concluded that the UA-751 was no better than ordinary auscultation or the UA-251 (auscultatory) system.

Johnston and Shah compared the Takeda UA-751 with Hawksley Random Zero sphygmomanometer (HRZS) measurement in only 10 patients (63). The resting systolic blood pressures ranged only between 90 and 122 and the diastolic between 57 and 81 mmHg. They found no systematic difference in pressure determined by the automatic or manual method. The standard deviation of the mean difference between the two devices was 3.8 for systolic and 3.6 mmHg for diastolic blood pressure.

In an important study Imai and colleagues assessed the accuracy and reliability of blood pressure values by comparing 8 automatic or semi-automatic devices designed for home blood pressure measurement (4 microphone/auscultatory devices and 4 cuff-oscillometric devices) with values obtained using standard sphygmomanometry (64). One of these instruments was the UA-751. They studied 89 subjects (systolic pressure 99—221; diastolic pressure 62—122 mmHg).

The mean difference in blood pressure values obtained using the UA-751 and standard auscultation was +4.11 (SD 5.60) and −0.40 (SD 7.75) mmHg for systolic and diastolic blood pressures respectively. These differences were greater for systolic blood pressure but less for diastolic blood pressure than the other devices tested (Omron HEM 439, microphone; HEM 719K, microphone; HEM 401C, oscillometric; Nissei DS 91, microphone; Sharp MB 305H, oscillometric; MB 500A, oscillometric; Matshushita Denko 260, oscillometric). With devices using microphone/auscultatory methods the systolic blood pressure values obtained coincided well with those obtained with the auscultatory method. However, a proportion of errors, on occasion as much as 25 mmHg, were noted for diastolic blood pressure values. This was usually attributable to an auscultatory gap or to a weak Korotkov sound after Phase IV. With devices using cuff-oscillometric principles the mean differences (and SD) for systolic blood pressure values were relatively greater than those obtained with the auscultatory method. For diastolic blood pressure there were minimal mean differences and a constant standard deviation of mean difference compared to the auscultatory method.

The authors recommended the development of equipment which employs the auscultatory method for systolic pressure and the oscillometric method for diastolic blood pressure to minimize these differences. They warn that practitioners should evaluate the difference in blood pressure values obtained using the auscultatory method and the device at least once in each patient (64).
Jamieson and colleagues assessed the agreement between the A & D UA-751 device and the HRZS (65). Simultaneous, same arm recordings were obtained in duplicate with both methods in 200 subjects in the ranges 92–221 for systolic and 51–121 mmHg for diastolic blood pressure by 3 observers against two A & D UA-751 devices. Agreement between the methods was acceptable according to the criteria suggested by the AAMI in the majority of comparisons. The mean differences between the UA-751 and observers ranged from −0.9 to 1.4 mmHg for systolic blood pressure (SD of differences 4.6–9.8) and −0.6 and 1.3 mmHg (SD of differences 2.9–5.1) for diastolic blood pressure although sizeable differences were seen in individual subjects. The authors concluded that the A & D UA-751 is an acceptable alternative to conventional sphygmomanometry and is suitable for routine clinical and limited research use, including intermittent home recording.

Devices using the Doppler principle

The Arteriosonde was pre-eminent for some years after its introduction. The Arteriosonde series are bulky and have not found much continuing support for use in routine clinical practice or research. The instrument is connected by a cable assembly to a standard sphygmomanometer cuff which incorporates the ultrasound transducer which contains a series of ultrasound generators and receivers. The cuff inflates and deflates automatically at a pre-set rate. When the cuff and brachial artery pressure are the same, vibration in the arterial wall causes a Doppler signal which is read as the systolic pressure. Diastolic pressure is recorded as the point at which pronounced diminution in arterial wall motion occurs. The different Arteriosonde models have been extensively evaluated.

Labarthe and co-workers undertook an early evaluation of the Arteriosonde 1010, Arteriosonde 1216, Boston automatic recorder (auscultatory method) and two further models against the Hawksley Random Zero sphygmomanometer (HRZS) and the standard sphygmomanometer using a Latin square design (16). None of the devices compared favorably with the standard machine, as judged by mean values of multiple readings for each of the two specimens of each device. In a series of paired readings, all but one of the automated machines showed marked deviation from readings with the standard mercury column sphygmomanometer. The authors expressed their disappointment with the state of the art and concluded that none of the automated devices could be recommended as a substitute for the standard sphygmomanometer.

George and colleagues reported on the use of the Arteriosonde 1217 and compared it with the HRZS and LSH sphygmomanometer using a random order of allocation of devices (66). The Arteriosonde gave similar values for systolic blood pressure to the other instruments, but diastolic blood pressure lay midway between Phase IV and V.

In 1975, Whyte and colleagues evaluated the Arteriosonde against intra-arterial measurements in 20 children in the postoperative period after cardiac surgery (67). Systolic pressures were very similar, but diastolic pressures were significantly overestimated with a mean difference of 6.25 mmHg (range +24 to −10). These
authors concluded that in their hands it did not give precise measurements for diastolic blood pressure.

Waikkakui and Prakanrattana compared conventional sphygmomanometry with Doppler 915 and direct intra-arterial measurements in 75 patients undergoing cardiac surgery in non-randomized order (49). The Doppler device produced systolic pressures that were lower by an average of 9.7 mmHg.

Linden and Wright compared the Arteriosonde with a standard sphygmomanometer in 15 patients using a factorial design (53). The Arteriosonde systematically produced higher diastolic pressures (7.4 mmHg) than the mercury sphygmomanometer.

III. SUMMARY AND CONCLUSIONS

In summary this chapter has stressed the importance of training observers in the measurement of blood pressure and of maintaining the devices in a satisfactory condition. It has also outlined the strengths and weaknesses of mercury column, aneroid, London School of Hygiene and Hawksley Random Zero sphygmomanometers. The state of play in the rapidly developing scene in respect of semi-automated devices has been summarized. Attention has been drawn to the clear need to evaluate such devices, preferably using recommended guidelines and independent observers (21, 22).

We conclude that for the present:

- For the measurement of blood pressure in routine office practice in the primary-care setting the mercury column sphygmomanometer, used appropriately by trained observers, remains the standard. The aneroid sphygmomanometer is an acceptable alternative, provided that it is serviced and re-calibrated regularly.

- For occasional blood pressure measurement in clinical research the mercury column sphygmomanometer is the benchmark against which alternatives have to be compared. Although the Hawksley Random Zero instrument is widely used and recommended, and has largely replaced the London School of Hygiene device, it has deficiencies. It systematically underestimates blood pressure, especially diastolic, and does not entirely eliminate bias.

- The semi-automated devices based on the auscultatory and oscillometric principles represent an important development in the evaluation of the blood pressure status of patients and in the evaluation of drugs used in the treatment of hypertension. The devices using ultrasound have been less widely taken up in clinical practice and research. Instruments incorporating the oscillometric or auscultatory principle appear to have some slight advantages in respect of repeated, accurate and reliable systolic, and diastolic blood pressure measurements respectively. Much collaborative work is required to ensure that all such devices under development and in production reach and continue to satisfy agreed standards of reproducible blood pressure measurement.
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4. Blood pressure measurement in clinical practice

Stephen N. Hunyor

Sound clinical skills are the major prerequisite for optimal measurement and interpretation of blood pressure in the clinical setting. Technological innovation has expanded opportunities for obtaining blood pressure readings, leading to reassessment of traditional diagnostic and therapeutic criteria. While standardized conditions of measurement are recognized as important in studies of pharmacological efficacy, increasingly stimulated blood pressures obtained during ambulatory recordings are seen as clinically relevant. The setting in which blood pressure is measured is equally important for interpretation of the results, as instanced by the differing connotation of the same reading in a pregnant woman and in a post-myocardial-infarction patient.

There is good evidence to support the need for duplicate readings on 3 occasions spread over 2 – 3 months in newly diagnosed mild hypertensives, prior to commencing pharmacotherapy (1, 2). The information from ambulatory monitoring will enhance our confidence in making a diagnosis and in instituting or altering treatment, but the end-points for such decisions have not been refined. The additional readings provided by this technique have the advantage of allowing treatment studies to be performed on smaller numbers of subjects, with greater reliability of conclusions. However, it should be noted that morbidity and mortality data on the effects of mild hypertension and the benefits of treatment are derived from casual office blood pressures. For more severe hypertension the superior predictive ability of ambulatory blood pressure measurement has been available for some time (3).

The fineness of the grain of blood pressure information required will vary according to the clinical setting. In some perioperative and intensive care situations continuous intra-arterial data remain the standard, although automated intermittent measurement with instruments such as the Dinamap (4) is challenging that role. More recently, new devices providing continuous readings by non-invasive means (5, 6) have further widened the options.

It is likely that in the future brachial pressure values will be complemented by study of pressure waveform and arterial stiffness. The difference between central and brachial pressures (7, 8), which is highlighted by the non-uniform action of some vasoactive agents (8), also deserves further study.
Contemporary National Standards (9–11) are now available to guide the manufacturers, purchasers and users of sphygmomanometers.

I. BLOOD-PRESSURE-MEASURING DEVICES

All semi-automated and automated blood-pressure-measuring devices are essentially based on one of 3 principles:

*Auscultatory* — detection of the onset and disappearance of Korotkov sounds (see below).
*Cuff oscillometric* — determination of the lowest cuff pressure at which maximum pressure oscillations occur in the air cuff (4). Systolic and diastolic levels correspond to cuff pressures at which the oscillations first increase and then cease to decrease. These end-points are approximated by extrapolative analyses.
*Volume oscillometric* — direct detection of the limb volume pulsation under the occlusion cuff, usually by an optical sensor. This technique is applicable only to small limbs, e.g. fingers, but has been used for ambulatory monitoring (12) and screening for hypertension (13). Systolic and mean levels only can be measured and diastolic is calculated, e.g. by a ratiometric method.

Additional strategies may enhance these methods, e.g. ECG gating, inclusion of infrasonic frequency spectra and band-pass filtering. Differential sensor techniques, where low-frequency signals from the cuff, common to both sensors, are subtracted from the epi-arterial sound signal can also enhance performance. Oscillometric technique accuracy may be enhanced by use of a dedicated high-impedance pneumatic line. Reliability can be further improved by repetition of failed measurements or by the ‘dual’ method where an auscultatory reading is ‘backed’ by an oscillometric.

The 3 principles of measurement rely on different vascular phenomena and cannot be expected to give identical readings. Korotkov sounds depend on a pressure-gradient to generate a flow phenomenon and generally underestimate systolic pressure whereas oscillometric devices, which principally measure mean blood pressure, give higher systolic readings because oscillations are transmitted from the patent artery above the cuff. Validation studies suggest that ambulatory monitors generally overestimate intra-arterial systolic pressure by 0–13 mmHg with a standard deviation of differences of 5.9–12.8. Diastolic pressure is overestimated by 0–8 mmHg (SD 3–11). Correspondence with standard auscultatory methods is somewhat better. Accuracy is degraded in those who are obese or have weak pulses, an auscultatory gap or loose skin. Muscle tension and a fast or irregular heart rate also lessen accuracy.

The automation of cuff pressure control has the potential for influencing the accuracy of devices, with the usual pressure reduction step being 3–8 mmHg, although the increment is governed by interpolative/predictive strategies. Accuracy is also influenced by cuff inflation rate (up to 30 seconds in some units), because a long duration of measurement will cause venous congestion.

Many studies use the T-tube method for making reference measurements which
produces bias in favor of the automated instrument, resulting in a 50% decrease in the number of observed discrepancies compared to the two-cuff or other arm method (14, 15). With most automated instruments the raw signal is not available for perusal and there is thus no indication of the quality of the data. Up to 10% of data are typically discarded according to criteria such as: diastolic pressure < 40 mmHg, systolic pressure > 255 mmHg, pulse pressure < 10 mmHg, abrupt increase in systolic pressure by > 40 mmHg or diastolic pressure by > 20 mmHg when not accompanied by an increase in heart rate.

II. POSITION OF THE PATIENT AND HYDROSTATIC FACTORS

As the reference point for arterial pressure measurement is the right atrial level, any 1 cm displacement of the site measured will alter the pressure measured by approximately 1 mmHg. Such discrepancies due to hydrostatic factors become more important as the measurement site moves peripherally.

The inaccuracies inherent in the measurement of blood pressure in the lateral recumbent position have been clearly recognized (16–18), and positional differences between the brachial artery and central aorta have been studied by Newton (19). The latter concluded that the uncorrected up arm pressures are 13–14/14–17 mmHg below the corresponding supine values, whereas hydrostatically corrected levels were within 3 mmHg, and that down arm pressures were inconsistent, suggesting that, besides hydrostatic effects, compression of the brachial artery by the patient’s body weight may have caused flow changes.

It is recommended that in the lateral recumbent position the upper arm should be used with appropriate hydrostatic correction. If measurement occurs at more distal sites, then the supine recumbent position is the position of choice.

Orthostatic effects

Orthostatic hypotension will go unnoticed unless standing readings are routinely performed. The preferred routine is to take a palpatory systolic reading during the first minute of standing, followed by the definitive auscultatory measurement at 2 minutes. It may take up to 20 minutes for an orthostatic effect to become evident. Many stand-alone instruments are limited by not taking standing readings.

Differences between sides

The systolic and/or diastolic pressure may differ variably by 10–20 mmHg between the two arms. A quarter of the population has a measurable difference, with the right arm being generally higher (20), related to the origin of the innominate arteries. Therefore, the right arm should commonly be used. This will also lead to the detection of the rare condition of pre-left subclavian coarctation. If the difference between the two arms is substantial and not transient, the presence of disease of the aorta or its large branches should be suspected, e.g. atherosclerosis of the aortic arch, Takayasu’s arteritis (aortic arch syndrome), aortic aneurysm, scalenus anticus syndrome, cervical rib or occlusion of the large arteries to the arm.
Differences between brachial and femoral arteries

In the supine person femoral systolic pressure is 10 – 40 mmHg higher than in the brachial. When systolic pressure in the popliteal artery exceeds brachial by > 20 mmHg, aortic regurgitation should be considered as the possible cause. The diastolic pressure, on the other hand, may be slightly lower at the femoral site (21) (Fig. 1). The higher peripheral systolic pressure is due to the conversion of potential energy and to summation with reflected waves which are influenced by the shape, situation and elasticity of the vessels (22).

The physician should at least palpate the femoral arteries but ideally should record the popliteal artery pressure of any patient whose reading is elevated in the right arm. In those with coarctation of the aorta the arm pressure will exceed that in the legs, whereas in those with aortic incompetence the femoral arterial pressure will be considerably greater. In general, vasodilatation diminishes the systolic pressure difference between brachial and femoral sites whereas vasoconstriction accentuates it. It is good discipline to measure the pressure in both arms and a leg in all hypertensive patients, at least initially. To measure pressure in the legs the patient lies on the abdomen and a thigh cuff is applied snugly to the mid-thigh. Some thigh cuffs have different top and bottom lengths to allow for thigh taper, or alternatively the cuff can be rolled on diagonally around the thigh.

III. KOROTKOV SOUNDS

The compression sounds of Korotkov (21) are heard over an artery distal to a compression cuff and vary in character as the pressure in the cuff is decreased to zero (atmospheric) pressure. They are divided into 5 phases (see Fig. 2).

The display (mercury column, dial, digital readout) indicates the systolic pressure at the moment that two consecutive Korotkov sounds are first heard during a slow deflation of the cuff. Generally, this is higher than the palpatory reading — in any case the greater of the two values is accepted as the systolic pressure. With continued

![Fig. 1. Intra-arterial pressure tracings showing the increase in systolic pressure as the recording site moves more peripherally. Redrawn from Burch and De Pasquale (21).](image-url)
Fig. 2. Left panel: Phases of the Korotkov sounds. Phase I begins with the sudden appearance of a faint, clear tapping or thumping sound that gradually increases in intensity. Phase II begins when sounds change to a murmur with a loud ‘swishing’ quality. Phase III begins when sounds assume a loud distinct knocking quality (less intense than Phase I). Phase IV begins when sounds suddenly become muffled and have a faint, murmur-like ‘swishing’ quality. Phase V begins when silence develops. The figure shows the end-points for both Phase IV and Phase V diastolic pressure. Right panel: Illustration of the auscultatory gap (details in text). Modified from Burch and De Pasquale (21).

deflation of the cuff the Korotkov sounds vary as shown in Fig. 2. The first diastolic pressure is recorded as the sound suddenly becomes muffled (beginning of Phase IV). The second diastolic pressure corresponds to the beginning of Phase V, i.e. the moment that the sounds finally disappear. If a definite diastolic end-point is difficult to obtain: let the pressure out of the cuff, elevate the arm for 5–10 seconds, inflate the cuff with the arm elevated, restore the arm to heart level and make a further measurement. If there is still difficulty, immerse the hand and forearm in warm water to induce vasodilatation and repeat (20). In general the pressure at the onset of Phase IV is approximately 10 mmHg above the diastolic pressure recorded directly.

The American Heart Association (23) has proposed the onset of Phase V (disappearance of sound) as the diastolic end-point. It is advisable to record both Phases IV and V, but the physician must decide which of the two to give greater significance.

Arguments for using the onset of Phase V include the difficulty of recognizing a definite change in the character of the sounds at the beginning of Phase IV and in some patients characteristic muffling of sounds does not occur at all.

Phase V can be particularly hard or impossible to detect in high-output states, e.g.
in children and in anemia, where Phase IV should be recorded. When Korotkov sounds are heard at zero pressure, the stethoscope may be pressing upon the brachial artery and deforming it.

**Auscultatory gap**

An interval of silence in the Korotkov sounds — the auscultatory gap — is observed in some patients, leading to an erroneously low systolic pressure (Fig. 2) if the compression cuff is not sufficiently inflated, or to an overestimated diastolic pressure if the first muffling of sounds is taken as the end-point. Such an error can be avoided by first recording the blood pressure by the palpatory method or by raising the cuff pressure to the top of the range and listening for Korotkov sounds throughout the deflation procedure.

The gap is more common in severely hypertensive subjects in whom a significant systolic pressure underestimation may have serious consequences. The mechanism is not fully understood but appears related to the downstream venous pressure which is influenced by very slow cuff inflation/deflation. The converse of the effect of a gap, when sounds are transmitted through the arterial circuit from prosthetic aortic valves, can lead to overestimation of systolic pressure.

**IV. CUFF SIZE AND CALIBRATION**

**Cuff size**

Inappropriately small cuffs can lead to blood pressure overestimation (Fig. 3) (24 – 28), a situation which can arise with the regular-sized cuff when the arm circumference exceeds 36 cm. With bandage cuffs, herniation of the bladder effectively reduces the cuff width.

Use of the correct cuff size has been simplified by the provision of ‘indicator lines’

![Diagram](image)

*a)*

**Fig. 3.** Effect of cuff size on transmission of sphygmomanometer cuff pressure to the underlying artery. Radiating lines show isobaric pressure zones where pressure on the artery approximates to that in the cuff. (a) In a thin arm even with a narrow cuff the full cuff pressure impinges on the artery, while a wider cuff leads to the same pressure reaching a longer length of artery. (b) With much intervening tissue the full narrow cuff pressure does not reach the artery, a situation corrected by widening the cuff. Modified from Smirk (20).
TABLE 1. Recommended bladder dimensions for blood pressure cuff (in mm) according to the American Heart Association*

<table>
<thead>
<tr>
<th>Size designation</th>
<th>Arm circumference at mid-point**</th>
<th>Bladder Width</th>
<th>Bladder Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>50 – 75</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Infant</td>
<td>75 – 130</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>Child</td>
<td>130 – 200</td>
<td>80</td>
<td>130</td>
</tr>
<tr>
<td>Small</td>
<td>170 – 260</td>
<td>110</td>
<td>170</td>
</tr>
<tr>
<td>Standard</td>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>240 – 320</td>
<td>130</td>
<td>240</td>
</tr>
<tr>
<td>Large</td>
<td>320 – 420</td>
<td>170</td>
<td>320</td>
</tr>
<tr>
<td>Thigh</td>
<td>420 – 500***</td>
<td>200</td>
<td>420</td>
</tr>
</tbody>
</table>

* From Ref. 23.

** Mid-point of arm is defined as half the distance from the acromion to the olecranon.

*** In persons with very large limbs, the indirect blood pressure should be measured in the leg or forearm.

which tell at a glance if the cuff is appropriate. Alternatively, the ‘TriCuff’ (29) provides in one multisize cuff the ability to vary appropriately the dimension of the inflated bladder, but has the disadvantage of relative bulkiness. The effect of cuff size on the accuracy of cuff oscillometric devices is not generally appreciated, nor do most such devices provide a selection of cuff sizes.

The requirements for cuff dimensions have been set out by the American Heart Association (23) (Table 1) and basically accepted by the American Standard (ANSI/AAMI) (9). However, the AAMI recommends a shorter bladder which extends at least half-way around the arm while recognizing that those covering greater than 80% of the circumference tend to give more reliable results (30). The width and length of a particular category of cuff (e.g. thigh) may vary widely according to country of origin with bladder dimensions ranging from 12 to 18 cm in width and 22 to 60 cm in length.

Recent recommendations of the Australian Standard (11) for the inflatable bladder size are shown in Table 2. A length of at least 60% of the maximal circumference of the limb and a width of 40 ± 10% of the mean circumference are deemed necessary.

Another approach to cuff size has been that of Maxwell (31) who noted the relative error from an inappropriate cuff and suggested a correction. This is an oversimplification which has not gained wide acceptance because it does not take into account the variable compliance of tissues under the cuff.

Cuff versus intra-arterial pressure measurement

Blood pressure measurement with compression cuffs is held to be less satisfactory than the intra-arterial methods because the former interferes with reflected waves (20, 32). It has been found (32) that if the brachial artery is obstructed distal to the
TABLE 2. Range of limb sizes and corresponding bladder dimensions (in mm)*

<table>
<thead>
<tr>
<th>Size designation</th>
<th>Limb circumference (± 10%)</th>
<th>Bladder Width (± 10%)</th>
<th>Bladder Length (± 10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>60 – 110</td>
<td>34**</td>
<td>66</td>
</tr>
<tr>
<td>Infant</td>
<td>100 – 190</td>
<td>58</td>
<td>114</td>
</tr>
<tr>
<td>Child</td>
<td>180 – 260</td>
<td>88</td>
<td>156</td>
</tr>
<tr>
<td>Adult</td>
<td>250 – 350</td>
<td>120</td>
<td>210</td>
</tr>
<tr>
<td>Large arm</td>
<td>340 – 470</td>
<td>162</td>
<td>282</td>
</tr>
<tr>
<td>Thigh</td>
<td>460 – 660</td>
<td>224***</td>
<td>396</td>
</tr>
</tbody>
</table>

* From Ref. 11.

** The 60% of maximum circumference and 40% of the mean circumference requirements yield dimensions for the newborn which do not agree well with the bladder sizes in conventional use. Typically a narrower bladder is used for newborns. In view of this, the requirements are relaxed for this category. A newborn bladder may have a width less than specified but in no case less than 25 mm.

*** Typically a narrower size is used for thighs. In view of this, the requirements are relaxed for this category but in no case should the thigh bladder width be less than 180 mm.

Point of measurement, the systolic pressure obtained directly may rise 20 – 30 mmHg.

Mercury column and cuff deflation rates

Mercury columns should be vertical (unless calibrated at an incline) and at eye level to avoid parallax. The mercury should move freely in a clean tube. The meniscus should come to rest on zero and readings should be to the nearest 2 mmHg, except when a London School of Hygiene or similar research instrument is used (33). Long rubber connecting tubes can lead to excessive ‘bounce’.

The ideal cuff deflation rate is approx. 3 mmHg/s, but automated instruments have pressure steps which start high, and progressively decrease (e.g. 8 to 3 mmHg). The accuracy of readings is dependent on the size of pressure steps as well as on heart rate. Variation in deflation rate from 10 to 3 mmHg/s can make a difference of 7 mmHg in a person whose true systolic is 149 mmHg with a heart rate of 60/min.

A suggested routine for blood pressure measurement is shown in Table 3.

Calibration of instruments

The ability to directly calibrate sphygmomanometers with a reference mercury column is essential. A T- or Y-piece connection should be provided for this purpose. The calibration procedure only tests the pressure-sensing element so that no check is applied to the detecting mechanism.
SI units

The Australian Standard requires that both SI units (kPa) and mmHg markings be applied with equal prominence on sphygmomanometers (11). The basic unit of graduation in the SI system is 0.2 kPa, which is almost 2 mmHg. The normotensive cut-off (140/90 mmHg) would become 18.6/12 kPa in SI units. The relationship between the two sets of units is shown in Figure 4. However, there is considerable opposition in many countries to the introduction of SI units for blood pressure measurement in clinical practice.

V. SELF-MEASUREMENT OF BLOOD PRESSURE

The World Hypertension League (WHL) (34) suggests that blood pressure readings taken in the home environment may be of greater value for confirming the diagnosis of hypertension, assessing effects of treatment, and engaging patients’ more active participation in a treatment program. However, there are no outcome studies or criteria for judging the normal range of home blood pressure, although the office cut-off of 140/90 mmHg is recommended.

Often home blood pressure is found to be useful for re-assuring patients and for enhancing compliance. It has been helpful in confirming that ‘borderline hypertensives’ maintain a higher home pressure than normotensives (35). Home pressure measurement has been partly supplanted by ambulatory monitoring and there are also concerns for self-measurement leading to inaccurate data. The WHL recommends self-measurement in selected patients as long as it is seen as only one part of an integrated patient care program.

TABLE 3. Blood pressure measuring routine*

- Position the person in a quiet environment, arm at heat level
- Place the manometer at eye level and close enough to read gauge markings
- Select the appropriate-sized cuff
- Locate the brachial artery and center the bladder on the mid-upper arm
- Determine the palpatory systolic pressure during progressive cuff inflation
- Rapidly deflate the cuff; wait 30 seconds
- Rapidly inflate the cuff to 30 mmHg above the palpatory systolic
- Position the stethoscope diaphragm over the brachial artery in the cubital fossa, close to or under the edge of the cuff
- Release cuff pressure at a rate of 3 mmHg/s
- Note the gauge reading to the nearest 2 mmHg when systolic and diastolic end-points are heard. Record posture, site of measurement and cuff size (if other than standard adult)
- Wait 30 seconds before repeating the procedure in the same arm
- On the first occasion of measurement and at subsequent intervals check the correspondence of readings in the two arms. Use the arm which gives the higher reading

* Modifications of this routine will be required with various semi-automated or automated devices.
Fig. 4. Diagramatic illustration of dual graduation markings (in kPa and mmHg) for sphygmomanometers (11). Mid- and full-scale markings are synchronous. Lower panel shows a segment of the detailed markings which cannot all be accommodated in this figure. Note that the current unit of graduation (2 mmHg) closely approximates 0.2 kPa in SI units.
VI. CONDITIONS AFFECTING MEASUREMENT

Pseudohypertension

Grossly calcified rigid arterial walls, mainly found in the elderly, can lead to pseudohypertension, where a gross error occurs in blood pressure measurement (36) (see Chapter 8, This Volume). While the prevalence of pseudohypertension appears to have been overstated (37), the finding of a palpable but pulseless brachial/radial artery after suprasystolic inflation of the cuff (positive Osler’s maneuver) (38) correlates with the presence of this condition.

Pulsus alternans

Pulsus alternans (21) consists of alternately strong and weak pulses due to a failure of all the ventricular musculature to contract with each alternate beat, and is a sign of severe depression of myocardial function (39). The most reliable detection of pulsus alternans and determination of its severity is as follows:

— Cuff pressure is raised above the palpatory systolic level.
— During slow deflation the Korotkov sounds are first heard at a rate precisely one-half the heart rate.
— With progressive decrease of cuff pressure the Korotkov sounds double in rate with the new sounds being less intense.

Pulsus alternans is exaggerated with aortic regurgitation, hypertension or decreased venous return caused by head-up tilting or nitroglycerin. Pulsus alternans should not be confused with alternations in force of ventricular contraction due to premature contractions, e.g. with bigeminy, where the feeble beat comes early.

The pressure difference between the first detection of strong Korotkov sounds and the later first detection of weak sounds allows quantitation of the degree of pulsus alternans (see Fig. 5).

Pulsus paradoxus

Pulsus paradoxus (21) represents an exaggeration of the normal (< 10 mmHg) decline in systolic pressure with inspiration and thus is really not paradoxical. The increase in pulmonary vascular capacity normally exceeds the inspiratory augmentation in venous return, leading to a temporary stasis of blood in the pulmonary vessels which decreases left ventricular pre-load and cardiac output.

With tense pericardial effusion, pulsus paradoxus is a frequent finding, whereas it occurs in about half the patients with constrictive pericarditis and is also observed in patients with emphysema or bronchial asthma (who have wide respiratory swings of intrapleural pressure) (40) and in those with hypovolemic shock, pulmonary embolus, pregnancy and extreme obesity. With pulsus paradoxus, inspiratory systolic pressure is decreased by more than 10 mmHg because deep inspiration cannot cause an increase in right ventricular filling due to mechanical restriction which may be accompanied by diaphragmatic pull on the pericardium.
Fig. 5. The phases of the Korotkov sounds as heard in a patient with pulsus alternans. At the higher pressure levels only the stronger beats produce audible sounds which start to alternate with sounds of lesser intensity as the cuff pressure is further lowered. See text for details. Modified from Burch and De Pasquale (21).

When pulsus paradoxus is marked (> 20 mmHg inspiratory decrease in arterial pressure), it can be determined simply by careful palpation of a peripheral pulse. Milder degrees can be detected only by sphygmomanometry. To detect pulsus paradoxus the cuff is inflated to suprasystolic levels and then deflated slowly, i.e. approx. 2 mmHg per heart beat. Peak systolic pressure during expiration is noted. The cuff is then deflated even more slowly and the pressure is noted when the Korotkov sounds can be heard throughout the respiratory cycle.

Reversed pulsus paradoxus, i.e. an inspiratory rise in pressure, can occur in hypertrophic obstructive cardiomyopathy (41).

VII. ‘WHITE COAT’ HYPERTENSION

Measurement of blood pressure in the office can cause considerable pressor reac-
tions, leading to overdiagnosis of hypertension and incorrect decisions to treat. In a large study of untreated patients with mild persistent elevations of clinic diastolic pressure (between 90–104 mmHg) one in 5 were found to have normal daytime ambulatory blood pressures, i.e. below the 90th percentile of a normotensive control group (42). Subjects with such a response were defined as having 'white coat' hypertension. Others consider that 'white coat' hypertension exists when the office reading (mean BP) exceeds the ambulatory figure by \( \geq 6 \) mmHg (43). Byrd and colleagues have also found the phenomenon to be reproducible and enduring (in 90%) (43). 'White coat' hypertensives were more likely to be female and younger, to weigh less and to be more recently diagnosed to have hypertension. They did not show increased blood pressure lability or an exaggerated pressor response while at work (42). The phenomenon was more pronounced when measurements were taken by a physician (44) and the biggest differences were between physician and technician and between daytime and sleep readings (14–10/6–1 and 24–15/18–12 mmHg respectively). The pressor reaction caused by the doctor's visit commonly waned in the first 4 minutes but was still significant at the tenth minute (44). Comparing nurse and doctor and using continuous intra-arterial monitoring it was found that the nurse's measurement caused only half the rise and practically faded away within 5 minutes.

VIII. AMBULATORY BLOOD PRESSURE MONITORING

Proposed indications for use of ambulatory blood pressure monitoring (ABPM) are shown in Table 4.

The mean difference between the highest and lowest pressures during the waking hours of a normal day in a group of normal subjects has been estimated at 35/23 mmHg. A pronounced diurnal variation is well documented with significant blood pressure falls during sleep. It has been recommended that an 8–12 hour recording (with half-hourly readings) is needed for a representative pattern of blood pressure behavior.

The potential utility of ABPM is indicated by the results in placebo-treated patients who were enrolled as mildly hypertensive in large therapeutic trials (1, 2).

**TABLE 4. **Indications for use of ambulatory blood pressure monitoring*

<table>
<thead>
<tr>
<th>Indications for use of ambulatory blood pressure monitoring*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Newly discovered mild hypertension (office DBP &lt; 100 mmHg, with no evidence of target organ damage) especially in those aged &lt; 50</td>
</tr>
<tr>
<td>• Borderline or labile hypertension</td>
</tr>
<tr>
<td>• Poorly controlled hypertension in confirmed patients on appropriate drug therapy</td>
</tr>
<tr>
<td>• Worsening end-organ damage despite apparently adequate blood pressure control</td>
</tr>
<tr>
<td>• As an adjunct to improve patient understanding of inadequate control and to improve compliance</td>
</tr>
<tr>
<td>• Evaluation of syncope or orthostatic hypotension in conjunction with Holter monitoring</td>
</tr>
<tr>
<td>• Suggestion of episodic hypertension or suspicion of pheochromocytoma</td>
</tr>
<tr>
<td>• Clinical research and drug evaluation</td>
</tr>
</tbody>
</table>

* From Ref. 45.
the first of these studies those with entry diastolic pressures of 90 – 104 mmHg had
a fall of 14/9 mmHg over 3 years on placebo, with 30% of the subjects falling below
90 mmHg. The baseline pressures had been determined from 4 readings at two
visits.

Ambulatory pressures correlate more strongly than do office or casual pressures
with echocardiographic or other indices of target organ damage (46 – 50). In a
follow-up of 1076 hypertensives by Perloff and colleagues (3) whose initial evalua-
tion included both ambulatory and office measurement, cardiovascular mortality
and morbidity were found to be significantly greater in those whose ambulatory
blood pressure was higher than expected from office readings. However, when con-
sidering the use of ABPM, it should be remembered that the present prognostic
standards are based on large population studies over several decades supported by
controlled clinical trials (see Chapter 14).

Even if ABPM is confirmed to be a more reliable predictor of hypertensive car-
diovascular damage, new standards of prediction of cardiovascular risk are required
for ambulatory blood pressure, as it is unproven that the standard values originally
used to calculate the risks indicated by casual pressures apply. The current rule-of-
thumb is that less than 10% of ambulatory readings should exceed a systolic
pressure of 140 or a diastolic of 90 mmHg. It should be noted that comparison of
24-hour non-invasive blood pressure with simultaneous invasive figures (44) has
shown underestimation by the former whether based on Korotkoff sounds or on
oscillometric measurement by 10(12)/4(8) and 8(13)/9(9) mmHg respectively. Elaborate criteria are unlikely to be of help in screening, diagnosing and treating
hypertension as it is too prevalent for mass application of ambulatory 24-hour
monitoring.

ACKNOWLEDGEMENTS

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5. Self-measurement of blood pressure

John P. Cox, Stevo Julius, Kevin O’Malley and Eoin O’Brien

The term ‘self-measurement of blood pressure’ has recently been defined in a statement from the World Hypertension League as ‘readings taken by lay persons on themselves or on a member of their family’ (1). Since patients usually determine their blood pressure at home, the technique is also called ‘home blood pressure measurement’. However, this latter term is not wholly appropriate, for the obvious reason that patients frequently measure their blood pressure at work and away from home. In any event, the terms ‘home measurement’ and ‘self-measurement’ are used interchangeably throughout the literature on this subject.

The term ‘home measurement of blood pressure’ has been used by some authors to include measurements taken by friends or persons known to the patient (2, 3), a circumstance which also comes within the remit of home or self-measurement. The term ‘home measurement’ must not, however, be used to denote blood pressure measurements obtained by researchers (usually doctors or nurses) in the subject’s home as, for example, in the Charlottesville Blood-Pressure Survey (4). Moreover, this term does not include measurements of blood pressure obtained by patients in their homes using ambulatory blood-pressure-recording devices requiring a high degree of patient co-operation (for example the Remler recorder where the patient inflates the cuff).

1. HISTORY

The first report of self-measurement of blood pressure is that of George Brown in the Annals of Internal Medicine, in 1930 (Table 1) in which he examines systolic blood pressure over a 3-year period in a 25-year-old man who had been trained to measure his own blood pressure (5). This paper is an important milestone in the development of self-measurement in the study of hypertension as not only does it make the point that a motivated patient can be easily trained to record his own blood pressure, but it also demonstrated a seasonal effect, namely, that blood pressure was lower in the summer months. Brown also reported for the first time
the use of self-measurement in the assessment of the effect of drugs (phenobarbital and potassium sulfinpyrazone) on blood pressure. Ten years later, the first paper demonstrating a difference between home and clinic measurement was published by Ayman and Goldshine (6). They compared measurements taken by relatives or patients themselves with recordings made in the clinic in 34 patients with essential hypertension and showed that patients recorded lower pressures than the physicians in their offices. Moreover, unlike Brown’s patient in whom only systolic pressure was measured, these patients were taught how to record both systolic and diastolic pressures.

In 1954, Fries reported that the blood-pressure-lowering effect of treatment was greater on home than on clinic measurement (7). He went on to suggest that ‘excessively high office pressures while under treatment are due to “escape” from the hypotensive effects of the drug during the time the patient visits the office or clinic.’ For these reasons he recommended home measurement as the technique of choice in the adjustment of antihypertensive drug dosages. In 1959, a blood pressure cuff incorporating a stethoscope endpiece in the inflation bladder was developed by Blaquier and Hoobler (8). It was designed so that the patient could slide it on like a bracelet to record his own blood pressure. This development facilitated patients in recording their own blood pressure by overcoming the practical difficulties of manipulating 3 items with two hands — the stethoscope endpiece, the manometer, and the inflation bulb for the cuff.

Julius and colleagues, using the self-measurement cuff described above, confirmed the accuracy of the technique of self-measurement of blood pressure in a study comparing self-measurement and clinic readings in normotensive males in 1964 (9). Ten years later, they used this technique to evaluate patients with borderline hypertension and showed that approximately 30% of these patients were hypertensive at home (10). In 1982, Cottier and colleagues confirmed the validity of using

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<td>Brown (5)</td>
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<td>1940</td>
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self-measurement of blood pressure in the assessment of antihypertensive drug efficacy when they showed that patients were able to detect small but reproducible changes in response to antihypertensive medication (−7/−5 mmHg for propranolol and −9/−7 mmHg for clonidine) using this technique (11).

In 1984, Kleinert and colleagues, in a comparison of self-measurement with 24-hour ambulatory monitoring and office measurement, concluded that although readings obtained on self-measurement were usually lower than those in the clinic, they did, however, reflect the overall level of blood pressure more reliably than office readings (12). Mejia and colleagues have recently established an upper limit of normal (142/92 mmHg and 131/85 mmHg in men and women respectively) for blood pressure measured using this technique in the Tecumseh Blood Pressure Study (13). The historical landmarks are summarized in the table.

II. METHODS AND DEVICES

The equipment used for self-measurement of blood pressure consists of a stethoscope, an inflatable bladder and cuff, and a measuring device. There are certain practical difficulties for the patient which include getting the cuff evenly wrapped around the arm, reading a manometer which cannot be placed at a convenient distance owing to the connecting tube being too short and the necessity of manipulating 3 items with two hands. Some of these problems may be overcome by incorporating the stethoscope in the cuff (8). Subjects with obese arms will need a cuff containing a bladder with the appropriate dimensions (14).

The effects of the muscle activity needed to inflate the cuff on blood pressure have been the subject of several studies. In a comparison of blood pressure measurements obtained first by a technician and then by the subjects measuring their own blood pressure, there was a higher level of blood pressure on self-measurement in most instances, with a marked increase in some cases (15). Veerman and colleagues have recently shown using finger blood pressures that the muscular activity required for cuff inflation results in an average rise in systolic blood pressure of 12 mmHg, while wearing an inflated cuff has no such effect on blood pressure (16). As this rise in systolic pressure takes on average 7 seconds and at most 21 seconds to return to baseline levels, self-measured systolic blood pressure may be overestimated to varying degrees dependent on the rates of deflation.

Devices for self-measurement of blood pressure

Devices for the self-measurement of blood pressure may be divided into two classes (17): portable instruments — for measurement in the home environment — and stationary machines — usually installed in public places.

Portable devices for self-measurement of blood pressure

There are 3 basic types — mercury, anaeroid and electronic. The mercury sphygmomanometer with a good-quality stethoscope has been shown to be the most accurate device available for the measurement of blood pressure (18). The mercury
sphygmomanometer can be readily modified for self-measurement of blood pressure (19), but most instruments used for home blood pressure measurement incorporate an anaeroid manometer with an inflating system, and a stethoscope. These devices are relatively inexpensive, but require that the subject has full use of both arms and also has good hearing and sight. Also regular calibration is required.

The newer electronic devices are easier to operate as they usually do not require the use of a stethoscope. Many of these devices are automated and just require the push of a button to inflate and deflate the cuff. They are, however, quite complex and are expensive. The ever-increasing availability of such ‘high-tech’ home blood pressure devices on the market bears testimony to the popularity of these instruments with patients.

However, while validation studies carried out by clinical researchers on devices used for self-measurement of blood pressure have shown some of them to be accurate (20–23), many are not (18, 23–27). Moreover, the criteria used for determining accuracy in validation studies are often not clearly stated and many validation tests used in the past would not meet contemporary requirements (18). Unfortunately, there is at present no legal obligation on manufacturers to comply with the standards that are available (28), namely the Association for the Advancement of Medical Instrumentation (AAMI) standard for automated devices (29), the British Hypertension Society protocol for evaluating automated and semi-automated devices (30), and the standards of the British Standards Institution which have been revised recently (31).

**Stationary automated machines**

Stationary automated machines, whether coin-operated or used free of charge, may be found at work sites, pharmacies, airports, and other public places. Evaluation of a commonly used automated coin-activated blood pressure device indicated (32) that blood pressure levels may vary considerably when one machine is compared with another, machine-recorded blood pressures may be 5–10 mmHg higher for both systolic and diastolic pressure compared to conventional measurement, and adequate educational material was rarely present at the site where automated machines were found. In the light of these problems with accuracy, it is difficult to see what role, if any, these machines have other than perhaps as a crude means of screening.

**III. TRAINING FOR SELF-MEASUREMENT**

Teaching self-measurement of blood pressure should be regarded as a medical intervention which requires commitment and time. It also requires a good relationship between patient and teacher, be it a doctor, trained nurse, or technician.

Physicians, however, are often reluctant to utilize self-measurement of blood pressure in the management of hypertension for a number of reasons. One concern relates to the putative negative effects of a patient knowing his or her blood pressure. While self-measurement does not appear to cause anxiety (5–7, 33–35), this has been objectively assessed in only one study (36). The experience at Ann
Arbor where the technique has been in use for almost 30 years has been that this effect is minimal and can be reduced by a judicious interview prior to the training of the patient (35). If investigators routinely inquire, following an explanation of the purpose and the advantages of blood pressure self-measurement, whether a patient really wishes to know more about blood pressure and whether having the information may cause a problem, about 5% of patients prefer not to know their blood pressures. Using such an approach, the problem of a patient becoming unduly concerned by the level of his daily blood pressure readings is rare.

The other, and probably most important, practical issue is the patient's ability to master the blood pressure measurement technique. This raises questions as to the number of patients capable of learning the technique, the educational level or intelligence of the subject and the length of time a physician or nurse should spend training a subject. The majority of studies have shown that it is feasible to train patients (3, 6, 13, 33, 36–39) or their relatives (2, 3, 6). In the largest of these — the Tecumseh Blood Pressure Study — 736 subjects were taught by a technician who visited them in their homes (13). During instruction subjects inflated and deflated the cuff while both the nurse and the subjects simultaneously listened through the same Y-connected stethoscope. The number of trials required before the measurement was considered acceptable, i.e. to values within 5 mmHg of the technician's readings, was recorded. For 608 subjects the average number of trials before an acceptable reading was achieved was 3.6 (range 3 – 10). The initial explanation usually lasted about 5 minutes and each trial required about 3 minutes. Thus, the average time investment was 20 minutes per person.

A subject's educational background did not affect the ability to learn the procedure. There was no significant relationship between years of education and the number of trials required before reaching an acceptable reading. However, a tendency for digit preference (rounding to 5 or 0) was detected among subjects with less than 12 years of education. In 3 years of work in Tecumseh where to date 940 subjects have been screened, not one individual has been found who was unable to learn the home blood pressure monitoring technique.

IV. REPRODUCIBILITY AND SENSITIVITY

While it has been shown that a subject can easily be taught to record similar readings to an observer, this, however, does not address the question of retention. In other words, do subjects continue to record reliable readings after the original practice sessions? Patients have been shown to retain the ability to record blood pressure accurately for as long as one (13) to two years (40) and relatives or friends for up to 3 months (2).

In a subgroup of 133 subjects in the Tecumseh Blood Pressure Study who repeated home blood pressure measurements one year after the first reading, average systolic pressure on self-measurement one year later was identical to the first (113.8 versus 113.7 mmHg) in contrast with a significant decrease from 115.4 to 110.4 mmHg in clinic systolic blood pressure (13). The average diastolic pressure on self-measurement was higher one year later (73.1 versus 71.6 mmHg, whereas clinic diastolic pressures were similar (76.6 versus 76.4 mmHg). Moreover, the intercor-
relations between the home systolic blood pressure taken a year apart were strong and did not change regardless of the number of readings, while those for self-measured diastolic blood pressure became weaker with lower numbers of readings suggesting that there is a lesser intrinsic variability with self-measured systolic compared with diastolic blood pressures.

The ability of this technique to detect small average changes in blood pressure has been demonstrated by Cottier and colleagues in a drug intervention trial comparing placebo to propranolol and clonidine where significant decreases in blood pressure of 8/5 and 11/7 mmHg, respectively, for both drugs were reported (11).

V. COMPARISON WITH OTHER METHODS

Isolated measurement of blood pressure usually taken in the clinic or office setting has been the universal technique employed in the assessment of blood pressure in medical practice. However, blood pressure measured in this way has serious limitations. Apart from potential error and inconsistencies in technique (41), and the large random variation in blood pressure (42), a measurement taken at one moment in the 24-hour cycle can hardly be expected to give a reliable indication of blood pressure behavior throughout the day. Moreover, the presence of the physician has a major influence on blood pressure recorded during a clinic visit (43, 44). Using continuous intra-arterial monitoring of blood pressure, Mancia and colleagues have shown that, in almost all of 48 hospitalized subjects studied, the doctor’s arrival at the bedside to take the blood pressure with a mercury sphygmomanometer induced immediate rises in systolic and diastolic blood pressures peaking within 1–4 minutes which persisted throughout the measurement procedure (43). Although repeated measurements by the doctor have little effect on the error of overestimation of blood pressure, it can, however, be reduced if the measurements are made by a nurse (44). There is little doubt but that the presence of the physician has a major influence on blood pressure recording during a clinic visit, and this is probably the chief explanation for the higher readings obtained in this setting.

Clinic pressures and self-measurement

The literature in this area has recently been reviewed in some detail by Pickering and James (45). The original observation by Ayman and Goldshine (6) that readings on self-measurement are usually much lower than clinic pressures has been confirmed in a number of studies (Fig. 1). Clinic pressures of patients with severe hypertension may be 20/10 mmHg higher than self-recorded readings, and clinic readings may also be higher than those taken in hospital by a nurse (46). In mildly hypertensive subjects clinic pressures may be 10/5–13/3 mmHg higher than those obtained by self-measurement (12, 47, 48). Kenny and colleagues compared blood pressures in patients with borderline hypertension on 3 occasions separated by two-week intervals using conventional clinic measurement, basal pressures, daytime ambulatory pressures and self-measured pressures (49). The clinic pressures were consistently higher than the self-measured, home, basal and ambulatory pressures — which did not differ significantly. The average difference between clinic and self-measured
pressures was 9/4 mmHg. In normotensive subjects the differences between clinic and self-measured pressures are much smaller (58). In another study of mildly hypertensive subjects, systolic pressures in the clinic were 15 mmHg higher than those obtained on self-measurement, whereas in normotensives the difference was only 2 mmHg (50). Julius and colleagues reported a mean difference of 14/4 mmHg between clinic and self-measured readings in a series of patients with borderline hypertension, but no significant difference (1/− 3 mmHg) in normotensives (10).

The well-established occurrence of a greater difference between clinic and self-measured blood pressures in patients with borderline hypertension than in normotensive subjects has important implications for practice (45). Since hypertension is conventionally defined by the level of blood pressure measured in the clinic rather than at home, individual patients who show an exaggerated blood pressure response in the clinic setting are likely to be identified as hypertensive. It is not clear why the clinic setting should raise blood pressure more in some individuals than in others. The anxiety associated with a clinic visit is the most obvious explanation, but there may be other factors involved (45) as studies have failed to show a correlation between the clinic/self-measured difference and psychometric evaluations of anxiety (47, 51). A number of studies have demonstrated the potent effect of the doctor—patient relationship on the patient's blood pressure (45). In a comparison of the effects of a personal interview, a word association test and the thematic appreciation test on blood pressure responses, the interview had the greatest effect (52, 53), which suggests that the extent of the response was a function of the degree of interpersonal interaction rather than the novelty of the situation. These and other studies (54, 55) support the view that the interaction between patient and physician is often sufficient to provoke a powerful pressor response similar to the defence reflex described in animal models.

![Graph showing comparison of clinic and self-measured systolic blood pressure.](image)

**Fig. 1.** Comparison of average levels of clinic and self-measured systolic blood pressure. Data from 10 published, 4 of which included more than one group of subjects. Reproduced with permission from Pickering and James (45).
Clinic, ambulatory and self-measured blood pressures

Pickering and James have recently summarized (45) the findings of 4 studies (12, 49, 56, 57) where comparisons between clinic, self-measurement and ambulatory blood pressure measurement have been reported. Home blood pressures were recorded by the patients and two studies included basal clinic pressures, measured after the patient had rested quietly for at least 30 minutes (49, 57). The average levels reported for clinic, self-measured and ambulatory pressures are given in Figure 2. These results show, firstly, that in all 4 studies the differences between the 3 measures were greater for systolic than diastolic pressure; secondly, that the differences in systolic pressure between clinic and self-measured recordings were greater than between self-measured and ambulatory readings; and, finally, that the differences in systolic pressure were greater in all the hypertensive groups than in the normotensive groups.

VI. NORMAL VALUES

While several studies have shown that values obtained on self-measurement are lower when compared with those on clinic measurement, there is relatively little information on what are considered to be ‘normal’ levels for blood pressure readings obtained in the general population using this technique. Frequency distribution curves for systolic and diastolic blood pressure for men and women in the fourth
decade of life (average age 32 years) based on data obtained on 608 healthy adults in the Tecumseh Blood Pressure Study (13). The mean (± SD) blood pressure was 121 ± 10/74 ± 8 mmHg for men and 112 ± 10/68 ± 8 mmHg for women. Based on these data, the upper limit of normal (i.e. the mean ± 2 standard deviations) is 141/90 mmHg in men and 136/86 mmHg in women. Interestingly, these findings for normal values on self-measurement are quite similar to those for day-time ambulatory blood pressure: 130 ± 11/81 ± 8 and 119 ± 11/76 ± 7 mmHg for males and females respectively (58).

VII. SELF-MEASUREMENT IN THE EVALUATION OF HYPERTENSION

In the assessment of the patient with hypertension, the diagnostic task is mainly concerned with quantifying the elevation of blood pressure, and hence the need for treatment. The doctor must decide whether the patient with elevated blood pressure is at sufficiently high risk of cardiovascular morbidity to warrant treatment. While there is a large body of data available to guide him, this is almost all based on clinic measurements (59–61). Although these data give a good estimate of risk for the population as a whole, the prediction for the individual patient is relatively weak. The clinician is therefore tempted to look for further measurements, preferably out-
side the clinic setting, using techniques such as ambulatory or self-measurement of blood pressure to improve the prediction. Unfortunately, there are few prospective studies of these techniques. The only large-scale prospective study published to date is that of Perloff and colleagues who demonstrated that ambulatory measurement of blood pressure was a better predictor of cardiovascular mortality and morbidity than clinic pressures alone (62). These findings, however, applied only to patients with mild hypertension (diastolic pressures < 105 mmHg), with no previous cardiovascular morbid events and who were under 50 years of age. An increasing number of other studies, which have been extensively reviewed elsewhere (63), have demonstrated that ambulatory pressures correlate more closely than clinic pressures with several different indices of target organ damage.

There is even less information available for self-measurement of blood pressure. No study yet has compared the prognostic values of self-measurement versus clinic measurement of blood pressure and very few have related self-measurement to the severity of target organ damage. Two studies have reported that an echocardiographically determined left ventricular mass correlated more closely with home than with clinic pressures (12, 64). However, when target organ status was assessed using minimal forearm vascular resistance as a measure of vascular hypertrophy (65) in the Tecumseh study (66), there were not substantial differences between subjects with 'sustained' and 'white coat' hypertension (those whose blood pressure is over 140/90 in the clinic but falls below the 80th percentile at home). These data would not support the use of self-measurement to distinguish between groups of borderline hypertensive patients with a lesser or greater risk of target organ damage as indicated by minimal forearm vascular resistance.

VIII. ROLE OF SELF-MEASUREMENT

There is some overlap in the information obtained between self-measurement and ambulatory monitoring. Self-measurement provides repeated measurements in the same situation over prolonged periods of time, and therefore is suited for monitoring changes in blood pressure induced by interventions or by the progression of hypertension, while ambulatory measurement provides information about the diurnal profile of blood pressure, and hence may be more suited for the initial evaluation of the patient.

It is difficult to define a more precise role for self-measurement in the diagnosis and evaluation of hypertension. While target organ damage (as indicated by echocardiographically defined left ventricular hypertrophy) may be more closely related to self-measurement than clinic blood pressure (12, 54), present evidence that self-measurement will provide a better predictor of an individual's complications in terms of morbidity and mortality from hypertension remains tenuous. Certainly, further research is required in this area.

This research could be carried out in the following stages. Firstly, it is necessary to develop age- and sex-specific normative values for self-measurement in large representative populations. Recently, normal values for self-measurement have been defined by Julius and colleagues (13) and for ambulatory measurement by O'Brien and colleagues (58). The next stage is to perform cross-sectional studies to
demonstrate that self-measurement of blood pressure shows a stronger association with target organ damage than isolated readings. To achieve this goal, however, sensitive markers of target organ damage are required. Thirdly, prospective studies are needed to show that measurements obtained using this technique are a stronger predictor of the complications of hypertension than clinic measurements and to establish new morbidity-based definitions of normal values.

The best advice for the present, however, is probably to use self-measurement of blood pressure as a complementary technique to clinic measurements. This technique is of special value in situations where ambulatory measurement is not available for individuals in whom the decision to treat is in doubt, when the clinical picture is not consistent with measured blood pressures, or when the response to treatment is unsatisfactory.

ACKNOWLEDGEMENTS

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6. Blood pressure measurement in childhood

Michael J. Dillon

The prevalence of hypertension in childhood is not clearly defined and depends on the definition of hypertension chosen. Although considerable variation is reported in the literature the true prevalence probably lies between 1 and 3% (1). The majority of these children will have mild increases in blood pressure and will come into the category of primary (essential) hypertension. A small number of children will have much higher blood pressures (10% of those with hypertension, 0.1% of the population) and will, in the main, suffer from secondary hypertension and be the ones that will require treatment.

However, for hypertension to be identified it is important to know what constitutes normotension. Pickering (2) stated that, if secondary hypertension is excluded, blood pressure is a continuous variable which is not obviously bimodal and hence hypertension at any age represents an arterial pressure above an arbitrarily defined value. In children this problem is further complicated by the physiological increase of blood pressure with age.

A number of population studies have been published giving normal values of blood pressure from infancy to adolescence. It is now accepted that blood pressure measurements repeatedly exceeding a given percentile (90th, 95th, 97.5th) (3, 4), or the mean plus two standard deviations, define hypertension rather than absolute values (1). However, in view of the variability in both conditions and techniques of measurement the available reference ranges are not directly comparable and this raises doubts about their validity when used to interpret blood pressure values in individual children. The problem does not arise when blood pressure is markedly increased but becomes important the closer the value approximates to what is considered normal.

1. METHODS OF BLOOD PRESSURE MEASUREMENT

The most convenient means of measuring blood pressure in children is the conventional sphygmomanometer. Of the various sources of error that are recognized with this technique the most important is cuff size. A cuff that is too small produces an erroneously high blood pressure recording and can occasionally fail to occlude the
underlying artery at all. A useful rule of thumb is to use the largest cuff, i.e. the widest cuff that still allows the vascular sounds to be heard easily with a stethoscope at the antecubital fossa. The length of the bladder should be at least two-thirds the arm circumference and preferably longer. To cover the age range 0 – 14 years a minimum of 3 cuffs is necessary with bladder dimensions 4 × 13, 8 × 18 and 12 × 35 cm (adult size). Secure fastening is essential and may not be possible with velcro, especially when using the small cuffs (5).

Systolic blood pressure measurement is preferred to diastolic blood pressure because of its greater accuracy and consistency. The fourth Korotkov sound, corresponding to the point of muffling as the cuff is deflated, is the best estimate of the diastolic pressure (3, 6). However, in some individuals (especially young children less than 1 year of age) the Korotkov sounds cannot be heard reliably whilst in others they are detected continuously almost to zero with no identifiable muffle on auscultation. In these circumstances alternative methods need to be used.

Instruments utilizing ultrasound based on the Doppler principle can record both systolic and diastolic pressures (6), but some doubt has been expressed about the accuracy of the diastolic estimate. In view of this some have advocated Doppler systems that only measure systolic pressure (7) which are more valuable for epidemiological purposes (8) and perfectly adequate for most clinical uses. The Park’s Doppler system is one such instrument and has the additional advantage over those that measure diastolic pressure as well in being relatively uncomplicated and inexpensive.

Alternative detection systems such as those that record low-frequency vibrations in arterial walls (infrasound) show unacceptable variability in measurement of diastolic pressure in children although they can measure systolic pressure accurately (6, 9). However, oscillometric blood pressure recorders such as the Dinamap monitors have been validated by comparison with intra-arterial measurements in infants and young children (10, 11) but do need to be calibrated regularly with reference to a mercury column, especially for epidemiological studies.

Other indirect methods of recording blood pressure including palpation of the radial or brachial arteries as a sphygmomanometer cuff is deflated only give gross estimates of blood pressure and the so-called ‘flush method’ provides, at best, a mean blood pressure measurement.

II. CIRCUMSTANCES OF MEASUREMENT

The child should be relaxed and comfortable and, unless contraindicated because of illness or age, should be sitting quietly for at least 3 minutes (5, 12). Measurements made when the child is eating, sucking or crying will be unrepresentative and usually too high. Ideally 3 measurements should be undertaken at 1-minute intervals with the arm supported at chest level and the third recording utilized. An acceptable ambient temperature is recommended and it should be appreciated that in newborns and young infants there is a significant difference between the sleeping and awake systolic blood pressure of up to 7 mmHg (13).
III. BLOOD PRESSURE STANDARDS

Although not precisely within the scope of this chapter, it would be remiss of the author to omit any mention of blood pressure standards in children. To allow interpretation of any blood pressure recording in a child reference must be made to an appropriate normal range and inherent in this are a number of major problems.

Blood pressure variance in childhood is dependent on a multitude of factors both genetic and environmental. It is clear that blood pressure increases with age during the pre-adult years and this occurs in all populations studied although the level and trend vary from population to population (14 – 17). Larger children (heavier and/or

![Graphs showing systolic and diastolic blood pressure percentiles for boys from birth to 12 months.](image)

90TH PERCENTILE
SYSTOLIC BP 87 101 106 106 106 106 105 105 105 105 105 105
DIASTOLIC BP 68 65 63 63 63 63 65 66 67 68 68 69
HEIGHT CM 51 59 63 66 68 70 72 73 74 76 77 78
WEIGHT KG 4 4 5 5 6 7 8 9 9 10 10 11

Fig. 1. (a) Age-specific percentiles of blood pressure measurement in boys, birth to 12 months of age. Reproduced from Ref. 4 with permission.
taller) have higher blood pressures than smaller children of the same age (18–24). It is therefore imperative that the level of a child’s or adolescent’s blood pressure is considered with respect to body size as well as to age.

Normative blood pressure data for children are available but have to be viewed with some circumspection since they may not reflect blood pressure norms for all racial groups and many tend to related blood pressure simply to age without making any allowance for size.

The National Heart, Lung and Blood Institute, Bethesda, has commissioned two reports of the Task Force on Blood Pressure Control in Children (3, 4). The first report appeared in 1977 and enjoyed wide distribution, becoming a major reference for blood pressure standards in children (3). The second report published in 1987 (4) used data taken from 9 different studies performed mainly in the United States although there was one British Source (the Brompton Study) included (25, 26). This

\[ Fig. 1. (b) Age-specific percentiles of blood pressure measurement in girls, birth to 12 months of age. Reproduced from Ref. 4 with permission. \]
second Task Force report has had several criticisms levelled at it, including the fact that, although extolling the virtues of several blood pressure recordings in an individual child before drawing conclusions concerning the height of the blood pressure, it eventually used the first blood pressure recording in the 70,000 subjects to prepare its standards (27). It also changes from using Korotkoff Phase IV (muffling) to Phase V (disappearance) for diastolic blood pressure at the age of 13 years. Abnormality is defined as systolic or diastolic blood pressure, or both, equal to or greater than the 95th percentile for age and sex on at least 3 occasions. In an attempt to incorporate the important contribution of body size into the analyses the Task Force has added the 90th percentile details of height and weight for normal children.

![Graph](image)

**Fig. 2.** (a) Age-specific percentiles of blood pressure measurement in boys, 1–13 years of age. Reproduced from Ref. 4 with permission.
at the bottom of the charts to help with the interpretation of blood pressure values of an individual child (4) (Figs. 1–3).

There are arguments in favor of generating percentile charts relating blood pressure to height (or some other index of body size) rather than age as have been incorporated in the charts produced by André and colleagues (28) in France and eliminating the errors of age-related percentiles and the resulting cumbersome technique to factorize for size (Figs. 4 and 5). It is hoped that such percentile charts will become more generally available and ideally relate more specifically to the populations that might use them. Meanwhile, knowledge of the shortcomings of age-related charts might eliminate misinterpretation of data, particularly during the phase of pubertal development when major discrepancies in body size occur.

\[
\begin{align*}
(b) \\
\text{SYSTOLIC BP} & \quad 130 \quad 125 \quad 120 \quad 115 \quad 110 \quad 105 \quad 100 \quad 95 \quad 90 \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \quad 10 \quad 11 \quad 12 \quad 13 \\
\text{DIASTOLIC BP (K)} & \quad 85 \quad 80 \quad 75 \quad 70 \quad 65 \quad 60 \quad 55 \quad 50 \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \quad 10 \quad 11 \quad 12 \quad 13 \\
\end{align*}
\]

90TH PERCENTILE
SYSTOLIC BP 105 105 106 107 109 111 112 114 115 117 119 122 124
DIASTOLIC BP 67 69 69 69 69 70 71 72 74 75 77 78 80
HEIGHT CM 77 89 98 107 115 122 129 135 142 148 154 160 165
WEIGHT KG 11 13 15 18 22 25 30 35 40 45 51 58 63

Fig. 2. (b) Age-specific percentiles of blood pressure measurement in girls, 1–13 years of age. Reproduced from Ref. 4 with permission.
Fig. 3. (a) Age-specific percentiles of blood pressure measurement in boys, 13–18 years of age. Reproduced from Fig. 4 with permission.

IV. WHEN TO MEASURE BLOOD PRESSURE

There seems to be little doubt that the blood pressure should be measured in all children presenting to clinicians when ill or when illness is suspected. This would be accepted practice in adult medicine and there is no reason why it should not be applied to children. There are special groups of children in whom it would be mandatory to measure blood pressure because of the known associations between certain pathological states and hypertension. Included in this category would be children with any form of renal or cardiovascular disease, urological abnormalities, meningomyelocele, abdominal wall abnormalities that may be associated with urinary tract pathology, neurofibromatosis and diabetes mellitus. In addition, children with headaches, visual symptoms, facial palsy, acute central nervous system disease,
Fig. 3. (b) Age-specific percentiles of blood pressure measurement in girls, 13–18 years of age. Reproduced from Ref. 4 with permission.

Guillain-Barré syndrome, dysautonomia, hypercalcemia, lead poisoning and acute hypovolemia should have their blood pressures recorded. Drug therapy with steroids, sympathomimetics, the contraceptive pill and intravenous administration of blood, plasma and saline must be monitored by blood pressure recordings. It would also seem prudent to record the blood pressure of children with a strong family history of hypertension (29).

V. BLOOD PRESSURE SCREENING

Screening for asymptomatic elevation of blood pressure in children could be justified on two grounds (30, 31). First, it will allow the detection of secondary hypertension due to potentially serious underlying disorders such as coarctation of the aorta, renal or endocrine disease prior to symptoms becoming apparent.
Fig. 4. Relation of blood pressure to height in boys. Reproduced from Ref. 28 with permission.

However, of the 1% or so of school children with a raised blood pressure only 10% (0.1% of the population) will have such hypertension and the remainder will have mild hypertension that will turn out to be, if anything, primary or essential. There are certainly advantages in detecting these severely hypertensive children, but the number detected by screening programs is likely to be very small (1 in 1000) for the effort that would be required.

The second ground for considering a screening program would be that it would detect children with mild increases in blood pressure who have an increased risk of
Fig. 5. Relation of blood pressure to height in girls. Reproduced from Ref. 28 with permission.

developing essential hypertension in adult life. Unfortunately the cost benefit ratio in identifying those with primary hypertension remains unclear (32). This conclusion is based on the analysis of tracking data in a number of studies in childhood (18, 21). Although it is known that some children maintain their peer rank order of blood pressure as they mature, there are others who increase or decrease their rank order (33). The correlation coefficients between initial and follow-up blood pressure levels in a number of studies are relatively low and insufficiently consistent to allow predictions of future blood pressure levels from initial recordings, especially in young children (34, 35). However, this may not apply in adolescence where blood
pressure recordings in the upper quintile of the normal range for age or size may have greater predictive value for future hypertension than in early childhood. The British Hypertension Society Working Party on Blood Pressure Measurement and the Joint Working Party on Child Health Surveillance have both considered this issue and neither recommended that there should be mass screening for blood pressure at school medical examinations (5, 27, 29, 31).

In the United States the Task Force also takes this view by not recommending mass community screening programs for children and adolescents (4). It does, however, focus on surveillance of blood pressure of children under continuous care by primary physicians and recommends, in accordance with the guidelines of the American Academy of Pediatrics, annual determinations of blood pressure in children by their primary physicians. These somewhat ambiguous messages might cause confusion but are of no relevance in countries where primary physicians are predominantly concerned with treating the sick rather than undertaking health checks on healthy children.

VI. AMBULATORY BLOOD PRESSURE MEASUREMENTS IN CHILDREN

As in adult practice, concern has been expressed about the value of casual blood pressure readings obtained in surgery or hospital environments. In view of this a number of studies have been undertaken utilizing portable semi-automated blood pressure recorders in children (36, 37). A number of devices have been used, including the Remler M2000 (Remler Corp., San Francisco), and certainly for adolescents have been tolerated with an acceptable level of compliance. Studies have confirmed that ambulatory blood pressure measurements are useful in the context of patients referred with suspected hypertension who in their normal environments during normal daily activities are normotensive (37). From a practical point of view such measurements are only feasible in older children and there is still some uncertainty concerning the interpretation of data and what proportion of blood pressure recordings over a study time base above the 95th percentile for age constitutes pathology. This is especially relevant when attempting to identify which labile hypertensive adolescents will go on to develop sustained hypertension in the fullness of time.

VII. PARTICULAR PROBLEMS

The most important hurdle to overcome in relation to blood pressure measurement in children concerns the decision to actually take the blood pressure. This investigative procedure is frequently omitted either because it is not perceived to be important or because the equipment to undertake it is unavailable or inappropriate or because there does not appear to be time available for such refinement in a busy clinical setting. To offset these difficulties, all those involved in the medical care of children must be made aware of the importance of blood pressure recording in children and an appropriate range of equipment must be made available. At least mercury sphygmomanometers should be provided with a range of cuffs suitable for
children and perhaps a nomogram of normal blood pressures from infancy to adolescence. Although expensive, in centers where blood pressures will be recorded in young children, especially those less than 1 year of age, some form of ultrasound or oscillometric device should be available. The Doppler machines that just record systolic blood pressure utilizing an ordinary sphygmomanometer and cuff would be more universally acceptable than sophisticated equipment recording diastolic pressures as well.

REFERENCES

7. Blood pressure measurement in pregnancy

Michael de Swiet

The diagnosis of hypertension in pregnancy has very serious consequences. It is often made on the basis of a single measurement of blood pressure made by a midwife using conventional sphygmomanometry. If the blood pressure is considered to be elevated, the patient is likely to be admitted to hospital for a minimum of several days which is very upsetting for her and her family and expensive for the National Health Service or other care provider. Clinicians should therefore be aware of the potential inaccuracies of sphygmomanometry and other techniques and how these errors may be minimized. This chapter considers the errors specific to pregnancy, the changes in normal pregnancy and the effect of posture. The use of the ‘roll-over’ test to predict pre-eclampsia is also discussed.

1. CONVENTIONAL SPHYGMOMANOMETRY

In pregnancy as in the non-pregnant state, conventional sphygmomanometry remains the technique that is most frequently used for measurement of blood pressure and the technique that has been most extensively evaluated. All the constraints concerning the validity of conventional sphygmomanometry that have been considered in earlier chapters apply to measurements made in pregnancy. However, pregnancy causes additional problems. These relate to the hyperdynamic circulation whereby resting cardiac output increases by 40% (1) and also to less quantifiable variables such as changes in elasticity of blood vessels and in the fat and water content of the arm where blood pressure is measured. In addition, the large uterus causes postural changes in blood pressure partly by physically obstructing the inferior vena cava and aorta and partly because of the blood volume that it contains (perhaps as much as 1 liter).

Validity of blood pressure by conventional sphygmomanometry. Korotkov IV or V?

The standard for blood pressure measurement is the placement of an intra-arterial cannula connected to an electromagnetic transducer. Raftery and Ward (2) com-
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<td>( \bar{x} )</td>
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<td>Systolic</td>
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<td>+17.8 to -28.6</td>
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<tr>
<td>Korotkov IV</td>
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<td>8.8</td>
<td>+28.7 to -6.5</td>
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<td>Diastolic</td>
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<tr>
<td>Korotkov V</td>
<td>6.6</td>
<td>9.8</td>
<td>+26.2 to -13.0</td>
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* Author’s estimate.
pared intra-arterial measurements made by catheterizing the brachio-axillary junction with simultaneous sphygmomanometry in the same arm below the site of arterial puncture. A 14 × 17.5 cm cuff was used in combination with the London School of Hygiene sphygmomanometer. Fifty patients were studied.

As has been the case in studies in the non-pregnant state, conventional sphygmomanometry underestimated systolic blood pressure by about 5 mmHg and overestimated diastolic blood pressure by 11 mmHg (K-IV) and 7 mmHg (K-V) (Table 1). Since K-V is nearer to the true diastolic blood pressure and in general the difference is only a little more variable (SD of differences K-IV 8.8, K-V 9.8), K-V should be used rather than K-IV for the estimation of diastolic blood pressure. In practice, the difference between K-IV and K-V is not great [4.5 mmHg in the study of Raftery and Ward (2)]. The increase in variability of K-V comes from the few subjects where the Korotkov sounds can be heard at very low cuff pressures, sometimes even where there is no pressure in the cuff. K-V diastolic blood pressure then equals zero. This is seen in other conditions where there is a hyperdynamic circulation such as hyperthyroidism. It has been used as a reason for taking K-IV rather than K-V as the diastolic blood pressure in pregnancy (3). However, rather than abandoning the more accurate K-V for the vast majority of the population, it would seem more sensible to retain K-V; but where K-V is implausibly low, i.e. less than 40 mmHg, to use K-IV noting that K-IV has been chosen rather than K-V. This would be more than adequate for clinical use. In experimental studies, subjects where K-IV has been used would need to be analyzed separately or discarded or a separate analysis could be made based on measurements of K-IV in all subjects.

The relatively small mean differences between intra-arterial and sphygmomanometer blood pressure conceal alarmingly wide individual variations. For example, in the study of Raftery and Ward (2) the 95% confidence interval for the difference between sphygmomanometer K-V blood pressures and true intra-arterial blood pressures was +26 to −13 mmHg: i.e. the sphygmomanometer could overestimate diastolic blood pressure by 26 mmHg or underestimate it by 13 mmHg. It is not known whether these differences are consistent within patients or whether there is an element of random variability in the difference on different measurement occasions in the same patient. It is likely, however, that there is an element of between-occasion variability in the error of estimation of blood pressure by sphygmomanometry and this, in addition to the biological variation in blood pressure, emphasizes the necessity of making several measurements of blood pressure by sphygmomanometry before making clinical decisions.

Raftery and Ward (2) did examine the short-term variability in blood pressure making successive readings and compared the differences between successive intra-arterial readings and successive sphygmomanometer readings. They concluded that a 95% certainty of real change in intra-arterial pressure could only be detected when sphygmomanometer pressures changed by at least 12 mmHg systolic, 16 mmHg diastolic (Phase IV) or 11 mmHg diastolic (Phase V).

Ginsberg and Duncan (4) also compared intra-arterial and sphygmomanometer blood pressures in pregnancy. They made observations in 70 women, 8 of whom were normal; the remainder had a variety of complications including severe hypertension. They first used a standard sphygmomanometer (cuff size not stated) and then recorded brachial intra-arterial pressure in the same arm at the elbow. In
contrast to the study of Raftery and Ward (2) they found that sphygmomanometry overestimated both systolic blood pressure (by 6 mmHg) and diastolic pressure (Phase V) by 15 mmHg (Table 1). Milsom and colleagues (5) compared intra-arterial pressures measured in the right arm with conventional sphygmomanometry pressures measured in the left arm in supine, right and left lateral positions in 10 pregnant patients. The cuff size was 35 × 12 cm. The weakness of this otherwise excellent though relatively small study is that no data are given to show that there were no systematic differences in blood pressure between the two arms. They found that sphygmomanometry consistently underestimates both systolic and diastolic blood pressure by 7 and 6 mmHg respectively (see Table 1). Calculations from the given standard errors of the differences suggest that the 95% confidence limits for both differences would be about 0–16 mmHg for systolic and −2 to 14 mmHg for diastolic (Table 1). We therefore have 3 studies suggesting that sphygmomanometry either overestimates both pressures (4), underestimates both pressures (5) or underestimates systolic and overestimates diastolic pressure (2). The circumstances of both direct and indirect blood pressure measurement between the 3 studies is so variable that it is impossible to reconcile these differences by allowing for any one difference such as cuff size, use of London School of Hygiene instrument rather than conventional sphygmomanometer, or site of arterial puncture. However, in the two studies where it is possible to know or estimate the 95% confidence limits for the differences between intra-arterial and conventional blood pressures, these are so large (Table 1) that the final conclusion must be that all studies are compatible with a difference between intra-arterial and conventional sphygmomanometer of ± 20 mmHg.

From a practical and clinical point of view, what is important is that epidemiological data and clinical decisions have been made on the basis of conventional sphygmomanometry. This should therefore continue to be used for clinical decision-making even if the pressures recorded by this technique are considerably different from intra-arterial pressure. Changes in blood pressure which are often the most clinically important feature are likely to be more accurately measured than the absolute level, since any bias should be operating in the same direction and with the same magnitude on each measurement occasion. But this will only occur if the measurement conditions for indirect blood pressure measurement are scrupulously standardized for known factors affecting the measurement. These include season of the year, time of day, time since eating, ambient temperature, subject activity, smoking, observer, relation of cuff size to arm circumference and posture. Many of these variables cannot be controlled in the clinical situation, but they should all be considered for research purposes.

**Cuff size**

One of the principles of sphygmomanometry and all other techniques of blood pressure measurement which depend on occlusion of the brachial artery by a cuff encircling the arm, is that the pressure inside the cuff should be transmitted completely to the artery: i.e. the artery should 'see' the same pressure as the manometer records as being present in the cuff. Inappropriate cuff size spoils this relationship. Usually the cuff is too small and the constricting effect of high pressure in the cuff
is dissipated through the tissues of the arm without being fully transmitted to the artery. Therefore a cuff that is too small overestimates blood pressure. In theory the cuff may be too large, constrict the artery too easily and underestimate blood pressure, but this is much less frequently a problem.

There have not been systematic studies in pregnancy comparing intra-arterial blood pressure with sphygmomanometer pressure at different cuff sizes. Raftery and Ward (2) using a single cuff 14 × 17.5 cm. found no correlation between the difference between intra-arterial pressure and sphygmomanometer pressure and arm circumference or adiposity (skin-fold thickness). Therefore they did not believe that cuff size was important. But they did not include many subjects with large arms. Ginsberg and Duncan (4) did not consider the problem and did not even quote the size of cuff that they used. Apart from the theoretical effects of changes in the water and fat content of the arm, there seems to be no reason for believing that pregnancy per se distorts the relationship between arm circumference and best cuff size for the determination of blood pressure. Under these circumstances it is reasonable to rely on studies such as those of Russell and colleagues (6), comparing intra-arterial pressure with sphygmomanometer pressure. Russell and colleagues (6) found that an ‘obese’ cuff measuring 39 × 15 cm gave more accurate results than a standard 23 × 12 cm cuff.

Other measurement techniques

There has always been concern that the blood pressure measured in the ante-natal clinic is not representative of the blood pressure at other times and that the anxiety of attending the ante-natal clinic causes a variety of ‘white coat’ hypertension induced by medical and nursing staff and the hospital atmosphere. For this reason, several studies have evaluated blood pressure recordings made by the patient herself at home.

Rayburn and colleagues (7) studied patients who used an aneroid sphygmomanometer at home. They were instructed in its use by a nurse using a stethoscope with two sets of ear-pieces so that the Korotkov sounds could be heard simultaneously by both instructor and patient. In a group of 59 patients with non-toxemic hypertension in pregnancy, average blood pressures at home were less than clinic pressures in 40% of patients, the same in 53% and higher in only 7%. Rayburn and colleagues (7) felt that the information gained from home recordings allowed antihypertensive therapy to be withheld from between 18 and 26 of the 59 patients. Dalton and colleagues (8) have developed a technique for transmitting home blood pressures recorded by sphygmomanometry directly over telephone circuits to the base hospital for subsequent computer analysis. These authors also felt that this technique enabled patients with hypertension to be safely monitored at home rather than in hospital.

The Dinamap instrument for automated indirect blood pressure measurement using oscillometry has also been evaluated in pregnancy (5). In 10 subjects intra-arterial pressure in the right arm was compared with Dinamap and conventional sphygmomanometry pressures in the left arm. As already noted, the major weakness of this study is that no data are given to show that there were no systematic differences between blood pressures in the two arms of the relatively small numbers
tested. Compared with intra-arterial pressure, the Dinamap instrument underestimated systolic blood pressure by about 7 mmHg and diastolic blood pressure was also underestimated by about 6 mmHg. But in this study conventional sphygmomanometry also underestimated systolic and diastolic blood pressures by 8 and 6 mmHg respectively, so that there were no overall differences between Dinamap and conventional sphygmomanometry. Since clinical decisions and epidemiological data have been based on conventional sphygmomanometry in the past, the Dinamap would appear to be a reliable automated substitute for conventional sphygmomanometry for clinical purposes. In the study of Milsom and colleagues (5) data were not given for the 95% confidence limits for the difference between individual Dinamap and intra-arterial readings. However, since the standard error of the difference was about 0.6 (n = 50) the 95% confidence limits are likely to be about 0 to 16 mmHg systolic and -2 to 14 mmHg diastolic, the Dinamap usually underestimating when compared with intra-arterial pressures.

Kirshon and colleagues (9) have also compared Dinamap with intra-arterial pressure recordings in 12 patients within 12 hours following delivery. Again the Dinamap underestimated systolic blood pressure by 9 mmHg, but there was no difference in diastolic blood pressure values. Since no data for the variability of the differences are given, it is difficult to estimate the error of individual recordings. However, the correlation coefficients between intra-arterial and Dinamap pressures were 0.90 and 0.96 for systolic and diastolic pressures respectively. These are of the same order of magnitude as found by Milsom and colleagues (5), implying that the range of errors of individual measurements is likely to be about the same.

Hon (10) has described a system used in 2 pregnant patients whereby a beat-to-beat record relating to blood pressure can be obtained by a transducer mechanically coupled to the skin at the wrist or over a finger. This transducer responds to the distortion produced at these sites during each cardiac cycle. This is a promising way of monitoring individual patients for short periods of time during an intensive or research situation. But more data are needed concerning the consistency of calibration.

II. POSTURE

Most clinicians measure blood pressure in pregnant patients seated at their consultation desk, lying supine or semi-supine on the examination couch or in the left lateral position if there is fetal distress in labor.

Important facts to consider with regard to the possible variation between the blood pressure measured in these positions are: (a) In a few patients in the last few weeks of pregnancy the uterus may obstruct the inferior vena cava, reduce venous return and hence cardiac output and cause a marked and often symptomatic reduction in blood pressure. (b) When measuring blood pressure with a sphygmomanometer, it is usually assumed that the aim is to measure the central arterial pressure. To do this the sphygmomanometer cuff must be on a horizontal level with the heart. If the sphygmomanometer cuff is on the right (upper) arm in the left lateral position the arm will rotate above the heart and this purely by a hydrostatic effect will cause the recorded blood pressure to be lower than when the patient is in the supine posi-
tion. In addition, the rise in blood pressure on changing from the left lateral to the supine position is the basis for a test that is said to predict the future development of pre-eclampsia, the 'roll-over' test.

There have been at least 5 studies where sphygmomanometry has been used with the cuff on the right arm to investigate the pressure difference between supine and left lateral positions (3, 5, 11 - 13). In all cases the pressure recorded was lower in the left lateral position by 5 - 18 mmHg. In two studies (11, 13) where the pressure was measured in the lower arm the pressure was 1 mmHg higher in the left lateral position than in the supine position. These observations suggest that any change in apparent pressure on moving between lateral and supine is likely to be artifactual and due to hydrostatic effects. It is not easy to estimate these effects accurately in patients in the lateral position and I therefore suggest that this position should not be used for blood pressure measurement except in emergencies. In the majority of patients who do not have supine hypotension there is very little (less than 3 mmHg) difference between supine and sitting blood pressures. To allow for the few patients who may have overt or covert supine hypotension, it would seem sensible to measure blood pressure in pregnancy sitting or semi-sitting whenever possible.

III. THE 'ROLL-OVER' TEST

It is well established that patients who will develop pre-eclampsia later in pregnancy are relatively sensitive to the pressor effects of infused angiotensin very early in pregnancy, from about 14 weeks of gestation (14). Infusing angiotensin is invasive and time-consuming, so it was postulated that it might be possible to substitute a natural increase in angiotensin level stimulated by turning the patient over from the left lateral to the supine position. Patients who will develop pre-eclampsia in later pregnancy should show an excessive rise in blood pressure when rolling over from the left lateral to the supine position. This was the basis of the roll-over test (15). However, it is now realized that the majority of the rise in blood pressure on turning over from the left lateral to the supine position is due to the hydrostatic effect caused by measuring blood pressure in the superior arm (see above). Subsequent studies have not confirmed the predictive power of the 'roll-over' test (11, 16 - 18) and it has therefore become discredited.

IV. CHANGES IN BLOOD PRESSURE DURING NORMAL PREGNANCY

There have been relatively few studies of blood pressure change in normal pregnancy and many have been biased by preconceived opinions concerning what is normal blood pressure and what represents a rise in blood pressure due to pre-eclampsia. For example, in the study of Andros (19) 300 women had serial measurements of blood pressure made throughout pregnancy. The conclusion was that the blood pressure does not rise in normal pregnancy, which is not surprising since any woman who was found to have a diastolic blood pressure equal to or greater than 90 mmHg or systolic blood pressure equal to or greater than 140 mmHg was excluded from the study even if she had no other signs of pre-eclampsia. However, the same general
pattern has been found by all others, e.g. Schwartz (20) and MacGillivray and colleagues (21): a fall in both systolic and diastolic blood pressure averaging 5 mmHg with a nadir in the middle of the second trimester, rising to pre-pregnancy levels by term. These averages conceal wide individual variations and it is common for systolic and diastolic blood pressures to fall by as much as 15 mmHg in early pregnancy.

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8. Blood pressure measurement in the elderly

Franz H. Messerli and Roland E. Schmieder

Several studies have shown that the prevalence of hypertension in patients older than 65 years may be as high as 50% (1 – 4). Most clinical trials have found that hypertension contributes heavily to the development of cardiovascular disease in these elderly patients (5 – 8). Recently, the European Working Party on Hypertension in the Elderly (9) demonstrated that antihypertensive therapy was beneficial in elderly patients, clearly reducing cerebral and cardiac morbidity and mortality. Furborg and Black (10) have estimated that more than 40% of elderly hypertensive patients are treated regularly by antihypertensive therapy. However, an increasing number of critical questions has been raised recently regarding the identification, pathophysiology and treatment of hypertension in the geriatric population (11, 12).

I. VASCULAR, STRUCTURAL AND FUNCTIONAL FINDINGS AFFECTING BLOOD PRESSURE MEASUREMENT IN THE ELDERLY

The following is an attempt to outline some characteristic vascular changes that may influence blood pressure readings in the elderly patient. Systolic pressure has been identified as a more important risk factor for cardiovascular morbidity and mortality in the elderly hypertensive patient than diastolic pressure (13, 14). Consequently, great efforts have been made to identify the underlying pathogenetic mechanism of isolated systolic hypertension. A predominantly systolic blood pressure elevation results from an increase in stroke volume, a decrease in the compliance of the large artery, or a combination of these factors. In other words, isolated systolic hypertension results from: (a) a high stroke volume ejected into an elastic arterial system with normal Windkessel function: (b) a normal stroke volume ejected into a stiff arterial system with impaired Windkessel function: or (c) a combination of (a) and (b). An increase in stroke volume is commonly seen in athletes but is unusual in elderly hypertensive patients, most of whom are characterized hemodynamically by a low cardiac output caused by a fall in both stroke volume and heart rate. Thus, the disproportionate increase in systolic pressure in the elderly patient is usually the result of a decrease in arterial compliance. This may be due to the combination of hypertension and age-related mechanisms such as loss of elasticity and generalized
narrowing of the arteries. Plaque formation and its sequelae further contribute to the decrease of arterial compliance. All of these changes are greatly accelerated by arterial hypertension. The decrease in arterial compliance, in turn, further increases systolic pressure. In addition, the concomitant loss of Windkessel function in the aorta impedes left ventricular ejection and adds to the stroke work of the left ventricle.

These changes in vascular structure go hand in hand with changes in vascular function: with increasing age, a decline in the β-adrenoceptor responsiveness of vascular smooth vessel can be demonstrated (15). However, it has been shown that α-adrenoceptor responsiveness remains relatively unaffected by age (16). Thus, a given catecholamine outflow will elicit a predominantly α-adrenoceptor vascular response in an elderly patient, as opposed to a β-adrenoceptor response in a young patient. It has been well documented that advancing age leads to a loss of elastic fiber in the arterial wall, and the deposition of collagen, elastin, glycosaminolipids and calcium. Examination of autopsy specimens of the human aorta demonstrates that compliance decreases with age (17). Nevertheless, the relative contributions of aging and artherosclerosis to the decrease in arterial compliance remain unclear.

Clinical experience has shown that systolic pressure may remain within normal limits in patients with severe generalized artherosclerosis. In contrast, systolic pressure increases with age, and isolated systolic hypertension occurs in some African populations with a low prevalence of artherosclerosis (18).

II. EVALUATION OF THE ELDERLY HYPERTENSIVE PATIENT

There are a number of factors operating in the elderly that may cause difficulty in assessing blood pressure status (Table 1). These can be considered under two headings. Firstly, problems may arise in accurately measuring blood pressure by the conventional indirect method and this includes pseudo-hypertension and the auscultatory gap. Secondly, there may be difficulties consequent to altered blood pressure regulation, notably increased blood pressure variability.

Blood pressure variability

Blood pressure readings have been found to be much more variable in the elderly than in the young (19, 20). Therefore, not surprisingly, several authors have sug-

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<th>TABLE 1. Clinical variables that may cause difficulty in assessing blood pressure status in the elderly</th>
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gested that baseline blood pressure should be assessed by an average of at least 3 readings on 4 different occasions (2). Several pathophysiological conditions are believed to contribute to age-associated variability of blood pressure in elderly hypertensive patients.

*Baroreceptor reflex sensitivity*

Baroreceptor reflex sensitivity has been documented to be significantly depressed in the elderly. Thus, acute changes in arterial pressure were thought to be only insufficiently counteracted by the baroreceptors (21, 22). Recently, however, these findings have been criticized, since the investigated study population (comprising 81 normotensive and hypertensive subjects aged 19 – 66 years) included only one subject older than 60 years. A more recent study (23) found that hypertension had only a very limited influence on baroreceptor reflex sensitivity in elderly subjects. The baroreceptor reflex sensitivity index derived from Phase II of the Valsalva maneuver was significantly lower in the hypertensive elderly group than in the normotensive elderly group only when evaluated with the non-parametric statistical Mann-Whitney test (23). The baroreceptor reflex sensitivity index derived from Phase IV did not differ significantly between the two groups (23). Thus, longstanding hypertension seems to have a limited influence on baroreflex sensitivity in elderly patients.

*Osler’s maneuver and pseudo-hypertension*

As mentioned previously, elderly hypertensive patients are characterized by a decrease in compliance of the large arteries. Increasing stiffness of the arterial wall, however, is well known to be capable of interfering with blood pressure management. Cuff blood pressure values deriving from non-distensible peripheral arteries may therefore be higher than intra-arterial readings, a phenomenon known as ‘pseudo-hypertension’. With the help of a simple bedside maneuver, one can distinguish between pseudo-hypertension and true hypertension. The maneuver is performed by assessing the palpability of the (pulseless) radial or brachial artery distally after occluding the artery manually or by cuff pressure. The origin of this clinical maneuver goes back to Sir William Osler (24):

'It may be difficult to estimate how much of the hardness and firmness is due to the tension of the blood within the vessel and how much to the thickening of the wall. If for example when the radial artery is compressed with the index finger the artery can be felt beyond the point of compression, its walls are sclerosed'.

In patients with pseudo-hypertension, the cuff pressure is inappropriately high, compared with the intra-arterial pressure, due to excessive atheromatosis (25 – 27).

In a clinical study, elderly hypertensives were divided into two groups according to their classification as Osler-positive or Osler-negative. Patients classified as Osler-positive had falsely elevated blood pressure readings, with a difference of 10 – 54 mmHg between cuff and intra-arterial pressure (Fig. 1) (28). The indexes of arterial compliance were noted to be lower in Osler-positive than in Osler-negative
Fig. 1. Comparison of intra-arterial and cuff systolic (▲) and diastolic (▼) pressure in Osler-positive and Osler-negative patients. Osler-positive patients are to the left of the line of identity, indicating that cuff blood pressure systematically overestimates intra-arterial values in these patients. Reproduced with permission from: Messerli FH, Ventura HO, Amodeo C. Osler's maneuver and pseudohypertension. N Engl. J Med 1985; 312: 1548–1551.

subjects. Thus, in elderly patients in whom the cuff pressure is markedly elevated, arterial stiffness should be assessed by Osler's maneuver and, if it is Osler-positive, an intra-arterial blood pressure measurement should be obtained. The absence of fundoscopic and other signs of advanced hypertension in the presence of excessively elevated blood pressure readings should cause a higher suspicion of pseudohypertension.

Auscultatory gap

During deflation of the cuff when systolic and diastolic pressure are assessed, an auditory hiatus may occur. The Korotkov sounds may initially be heard at the level of the systolic pressure, then disappear, become audible again at a level of 30–55 mmHg below, and finally disappear completely at diastolic blood pressure levels. This auscultatory gap seems to be particularly common in patients with isolated systolic hypertension. The exact pathogenetic mechanism of this phenomenon remains unknown. It must be remembered in this context that the Korotkov sounds are the audible results of a collapse of the arterial wall that occurs whenever cuff pressure exceeds intra-arterial pressure levels. Once cuff pressure falls below intra-arterial diastolic pressure levels, this collapse no longer occurs. Conceivably, an auscultatory gap could result from various mechano-elastic properties of the arterial wall which prevent or mitigate this collapse to the extent that no Korotkov sounds can be heard. If these theoretical hemodynamic considerations are true, a hiatus of the Korotkov sounds would be another clinical sign of impaired compliance of the large arteries.

Whatever the mechanism, it should be remembered that in elderly patients cuff pressure should be inflated above systolic pressure. This can be verified easily by monitoring the disappearance of the radial pulse with progressive inflation of the cuff.
Postural hypotension

Postural falls in blood pressure may coexist in patients bearing the diagnosis of hypertension. It may be present ab initio or be precipitated by drug therapy. A postural fall in blood pressure occurs in approximately 10% of all otherwise healthy elderly subjects (29). Furthermore, such a fall in blood pressure may also occur in the presence of raised supine or sitting blood pressure. For example, approximately 11% of untreated hypertensive patients in the European Working Party on Hypertension in the Elderly study had a fall in blood pressure (30). In most cases such falls in blood pressure are not associated with symptoms and clearly can only be detected by measuring blood pressure in the supine and standing position. However, injudicious drug therapy including blood-pressure-lowering agents may aggravate the situation. It is therefore recommended that blood pressure be measured in the supine and standing positions on initial blood pressure evaluation in the elderly, but also after drug treatment has been commenced.

Pseudo-hypotension

Pseudo-hypotension is a rare entity characterized by inappropriately low cuff blood pressure measurements with regard to intra-arterial values. Pseudo-hypotension results most often from a high-grade obstruction of the subclavian or brachial arteries either unilaterally or bilaterally. Patients are characterized by hypertensive target organ disease such as left ventricular hypertrophy or nephrosclerosis in the presence of normal or below-normal blood pressure values. Usually other signs of artherosclerotic cardiovascular disease are present. Wide pressure differences between the two arms may be due to unilateral obstruction in the subclavian or brachial artery or a subclavian steal syndrome.

‘Cuff inflation’ hypertension

Most recently, Mejia and colleagues (31) reported 2 patients who experienced a marked rise of intra-arterial pressure during cuff inflation. In one, an increase of 40 mmHg systolic and 36 mmHg diastolic was observed during cuff inflation, during which intra-arterial pressure was monitored. It is unclear how common this phenomenon is among elderly hypertensive patients. The authors speculated that cuff-inflation hypertension was probably based on a reflex mechanism similar to that which causes blood pressure elevation during hindleg compression in dogs. Conceivably, the pain or discomfort of inflating a blood pressure cuff could lead to sympathetic stimulation and thereby elevate arterial pressure.

Postprandial hypotension

Blood pressure can vary considerably in relation to various stimuli, but it may not be generally realized that blood pressure may change substantially after a meal in the elderly. Lipsitz and colleagues evaluated the effect of a standard meal on blood pressure in the young and elderly and found a moderate to marked fall in the latter (32). Blood pressure started to fall during the meal and systolic blood pressure fell
by an average maximum of 25 mmHg. This fall in blood pressure did not occur in
the young control group. It should be emphasized that the study group was not only
ever but also institutionalized with multiple disease. Whether this finding would
be applicable to the elderly in general is questionable. While these findings are rele-
vant to patients with syncope, they also have a bearing on establishing blood
pressure status even in the conventional context of diagnosing and managing hypertensive in the elderly.

III. CONCLUSIONS

Elderly patients suffer predominantly from isolated systolic hypertension. While a
systolic pressure elevation has clearly been shown to increase cardiovascular mor-
bidity and mortality, the beneficial effects of lowering systolic pressure are less well
documented. Representative blood pressure measurements in elderly patients are
often difficult to obtain because these measurements are variable and involve a
variety of artifacts such as pseudo-hypertension, pseudo-hypotension, auscultatory
gap, cuff-inflation hypertension, etc. These difficulties make it mandatory to assess
blood pressure levels carefully by home blood pressure readings, 24-hour ambu-
latory blood pressure monitoring, and, if necessary, intra-arterial measurements.
Assessing target organ disease by echocardiography and evaluating renal function
may help to better quantify the impact of blood pressure levels in the elderly and
permit identification of patients who will benefit most from selective antihypertensive therapy.

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according to age, sex, blood pressure and previous cardiovascular disease in patients


9. Measuring blood pressure during exercise

Paul L. Padfield
and Sathya G. Jyothinagaram

Traditionally the assessment of blood pressure and the diagnosis of hypertension have been based upon a measurement taken in the rested condition, usually while seated. Such measurements have formed the basis of all intervention trials and the various guidelines set down regarding levels of blood pressure which dictate pharmacological intervention.

It has long been recognized, however, that such readings are variable and correlate rather loosely with ambulatory blood pressures (see Chapter 12). A natural extension of attempts to measure blood pressure in the ambulant setting is an assessment during more vigorous exercise and even the most sedentary of us will at times during the day undertake some forms of physical activity which are likely to result in short-lived but fairly major increases in blood pressure. This chapter will attempt to review the effects of exercise on blood pressure and the possible relevance of such changes in clinical medicine. As will be discussed, there is evidence to suggest that blood pressure responses to exercise may predict future hypertension in normotensive individuals, may confirm or refute sustained hypertension in those with more borderline resting levels and may correlate more closely with echocardiographic evidence of left ventricular hypertrophy than a casual measurement of blood pressure.

Clearly, a meaningful assessment of the exercise blood pressure response depends upon an accurate measurement of blood pressure itself and it is in this area where most difficulties have arisen. Non-invasive forms of measurement have proved less accurate than the direct intra-arterial assessment, thus posing problems in the interpretation of many studies.

Such a review would not be complete without some consideration of the role of the measurement of exercise blood pressure in current clinical practice. In some situations this may be well established as in the measurement of blood pressure during standard exercise testing of patients with suspected heart disease while others are more speculative such as the assessment of antihypertensive therapies during peak exercise. An attempt will be made to put into perspective what remains a rather
vague area for many practising clinicians, even perhaps for those with a particular interest in hypertension.

I. STATIC VERSUS DYNAMIC EXERCISE

It is conventional to attempt the separation of two different forms of exercise. One results in repetitive contraction of various larger muscle groups involving a change in the length of muscle fibers. Such exercise may be carried out over a period of minutes or even longer and is best exemplified by walking, running or cycling. This form of exercise is described as dynamic or isotonic in contradistinction to static or isometric exercise which involves a non-repetitive and more sustained muscle contraction without a change in muscle length. This is the form of exercise undertaken when lifting weights or pushing against a firm object.

Despite these rather rigid definitions it is clear that most forms of exercise in the real world will involve a combination of the two. It is however important to consider them separately, if only because the cardiovascular responses are somewhat different.

In the laboratory setting, dynamic testing is usually performed either with some form of treadmill test or by bicycle ergometry.

Treadmill testing involves a series of stepwise increments until maximum activity is reached as in the Bruce protocol (1). Sometimes a submaximal stimulus is used (2) and this may allow for an easier assessment of diastolic blood pressure when a mercury sphygmomanometer is used. A treadmill test will involve a significant isometric component in the upper limbs. This is minimized during bicycle ergometry where the arms can be more stationary, but both tests have been widely used.

Isotonic or static exercise is tested in the laboratory by means of a hand-grip. Protocols may vary but usually involve the assessment of maximal hand-grip strength followed by a more prolonged period of a specified proportion of the maximal activity for a fixed length of time (3).

The hand-grip test is much simpler to set up than either of the two dynamic tests and in some studies attempts have been made to determine whether similar information may be derived from both forms of testing (4).

II. CARDIOVASCULAR RESPONSE TO EXERCISE

Normal subjects

Lund-Larson and colleagues (5) studied 367 normotensive men measuring systolic blood pressure only, using the London School of Tropical Medicine and Hygiene Sphygmomanometer (6), during exercise on a bicycle ergometer. Subjects increased gradually to a maximum of 200 watts and exercised until fatigue or for 24 minutes. Blood pressure increased linearly with the level of activity until a peak systolic blood pressure of 195 ± 18 mmHg. Resting blood pressure was less than 144 mmHg in all subjects.

Franz (7) showed similar results with indirect measurement of blood pressure in
a group of 173 normotensive males and 150 normotensive females also using bicycle ergometry but on this occasion diastolic blood pressure was recorded at Korotkov Phase IV. Franz regarded the upper limit of the normal response to exercise to be 200/100 mmHg in both men and women calculated on the basis of the mean + 1 standard deviation. This would be rather similar to the values found by Lund-Larson and colleagues (5). Wolthius and colleagues (8) recorded a mean peak systolic blood pressure of 184 mmHg during exercise also using a mercury sphygmomanometer and an aggregate of this and similar studies would indicate that normal subjects would not be expected to increase systolic blood pressure more than 220 mmHg following vigorous exercise.

Other studies have also demonstrated an initial abrupt systolic blood pressure response which relates to the intensity of exercise (3, 9–12) and is paralleled by an increase in heart rate.

Diastolic blood pressure has not always been measured (13), but dynamic exercise usually produces little changes or sometimes even a fall in diastolic blood pressure (8, 14–16). These changes are accompanied by a marked fall in total peripheral resistance and an increase in cardiac output (13, 17). It seems likely that they are mediated predominantly via the sympathetic nervous system as changes in heart rate and blood pressure are closely paralleled by an increase in plasma norepinephrine (18). Some withdrawal of parasympathetic activity may also be involved in the increase in heart rate (19). The normally expected baroreceptor-mediated fall in heart rate as blood pressure rises appears to disappear as the pulse increases above 150 beats per minute (20). Systolic blood pressure falls abruptly after the cessation of exercise, reaching baseline values within seconds although heart rate takes longer to fall (3, 21). Indeed, as will be discussed later, the rapidity of this blood pressure fall is such that standard mercury devices cannot reliably record the changes. There seems little difference in the cardiovascular responses to either treadmill exercise or bicycle ergometry.

The blood pressure response to static or isometric exercise is different in that most studies have demonstrated a greater increase in diastolic blood pressure than that seen with dynamic exercise (22). Systolic and diastolic pressures increase in parallel and again are predominantly related to an increase in cardiac output (17, 23, 24). Peripheral resistance is much less affected by isometric exercise and thus diastolic blood pressure does not fall (17, 23). Overall the systolic blood pressure response to isometric exercise is probably somewhat less than that to isotonic or dynamic exercise, but mean blood pressure changes may be similar or even greater because of the diastolic increase (3).

The blood pressure response to exercise may be increased with age (7), although this is debated (8, 25–27), or in obese subjects (26).

Prior training may reduce the blood pressure response to exercise (28) and a period of ‘warming up’ prior to exercise (resulting in vasodilatation) may significantly limit peak blood pressure responses (3).

**Hypertensive subjects**

*Established hypertension*

Lund-Larson and colleagues (5) also studied 785 patients with mild elevations of
blood pressure (DBP < 110 mmHg but > 95 mmHg, SBP > 150 mmHg but < 180 mmHg) and showed an identical pattern of response to normotensive individuals following bicycle ergometry although the peak pressure at maximal exercise at 228 ± 15 mmHg was higher. A smaller group of 55 patients with more severe hypertension (SBP > 180 mmHg, DBP > 110 mmHg) increased SBP similarly but to a peak of 242 ± 25 mmHg. This and other studies indicate that the higher peak responses in hypertensive patients are simply related to the fact that basal blood pressure is higher (29, 30). As some have suggested that exercise pressure responses may be predictive of subsequent hypertension, it may not always be the resting blood pressure which is the major determinant of a response to exercise. There are often disproportionately large increases in diastolic blood pressure to both isotonic and isometric exercise (7, 31–33).

It has been suggested that hypertensive patients are less able to reduce total peripheral resistance during exercise, and hence have a greater diastolic response (2).

Following the cessation of exercise, patients with hypertension do not reduce blood pressure to normal values as fast as normotensive individuals and this again may relate to an increased total peripheral resistance (2, 34).

*Borderline hypertension*

As already indicated, the blood pressure response to exercise in patients with borderline hypertension is likely to be somewhere between that seen in normotensive individuals and those with more severe forms and this is indeed the case (4, 7). What does seem likely, however, is that the exercise blood pressure response may be a good predictor of the subsequent course of blood pressure and this field will be expanded later.

III. METHODOLOGY FOR MEASURING BLOOD PRESSURE DURING EXERCISE, INCLUDING COMPARISONS WITH INTRA-ARTERIAL METHODS

*Intra-arterial monitoring*

In order to record the rapid changes in blood pressure which are likely to occur during the onset and offset of vigorous exercise, continuous measurement would be ideal. Intra-arterial blood pressure measurements are obtained by means of a line inserted into the brachial artery connected to an external transducer. The so-called ‘Oxford system’ (35) based upon earlier work by Bevan and colleagues (36) has been used by most workers and remains the standard against which all other methods have to be compared. It must be remembered, however, that there are certain physical principles, including excessive damping of the trace obtained, which can alter the blood pressure recorded with these devices, so resulting in some inaccuracies (37, 38) (see Chapter 16).

The pattern of blood pressure changes in response to exercise as outlined above has been best demonstrated using intra-arterial techniques, as has the abrupt fall in blood pressure when exercise is stopped (3, 21). The complexity of this methodology
together with some inherent danger in cannulating an artery, has meant that intra-arterial monitoring of blood pressure during exercise has however been confined to few centers.

**Mercury sphygmomanometer**

Routine indirect measurement of blood pressure with a mercury sphygmomanometer is available to all and is used widely during exercise testing. Auscultation may result in inaccurate measurements in the setting of exercise, however. During both standard forms of dynamic exercise testing (treadmill or bicycle ergometry) some noise is involved and this is likely to impair the ability to precisely record both systolic and diastolic blood pressure. Diastolic blood pressure may be particularly difficult to record as the Korotkov sounds may not disappear (27, 29). Even in the situation of measurement at rest there are problems comparing mercury sphygmomanometer with intra-arterial blood pressure measurements (38) and such discrepancies are potentially greater during exercise.

The marked increase in variability of blood pressure seen during exercise (3) cannot be recorded by intermittent measurements and the time interval between the recording of the systolic and diastolic by auscultation will invariably mean that many cardiac cycles have taken place in between.

In 1954 Henschel and colleagues (40) studied 11 normal male subjects during treadmill exercise. They described an insignificant difference in systolic blood pressure measured intra-arterially in comparison to a standard mercury sphygmomanometer (Table 1). This statement requires some qualification, however, as although the mean difference was only 1 mmHg, the standard deviation of the difference was 12, indicating a wide scatter. The difference between methodologies for diastolic blood pressure was 52 ± 30 mmHg! Karleford and colleagues (9) did not attempt to record diastolic blood pressure non-invasively but had a much better relationship for systolic with a difference of 3.6 ± 2.4 mmHg.

Most studies reported recently confirm the inability to accurately assess diastolic blood pressure during maximal exercise (Table 1). Submaximal exercise may however be associated with fewer errors with indirect blood pressure measurement (41, 42). Careful training of observers may also improve the accuracy in these circumstances (39).

Despite these observations indirect sphygmomanometer measurements are routinely made during exercise stress testing in the assessment of patients with ischemic heart disease.

**Electronic ambulatory monitors**

Theoretically the use of non-invasive electronic ambulatory monitors should be more accurate in assessing blood pressure during exercise as all forms of observer bias would be removed. It may be argued that even if there was a systematic difference between an intra-arterial measurement of blood pressure and a non-invasive cuff measurement, this would be relatively unimportant, but random errors would be unacceptable. Unfortunately, the latter appears to be the case and little reliance can therefore be placed on data so obtained.
**TABLE 1** Comparison of intra-arterial and cuff measurements of blood pressure during peak exercise

<table>
<thead>
<tr>
<th>Study</th>
<th>(Ref. no.)</th>
<th>Subjects</th>
<th>Exercise</th>
<th>Difference in BP (IA-cuff) at peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henschel et al., 1954</td>
<td>(40)</td>
<td>11 normal males</td>
<td>Treadmill</td>
<td>$-1 \pm 12/52 \pm 30$</td>
</tr>
<tr>
<td>Karlefors et al., 1966</td>
<td>(9)</td>
<td>38 normal + hypertensive</td>
<td>Ergometer</td>
<td>$3.6 \pm 2.4$ (SBP) DBP not recorded</td>
</tr>
<tr>
<td>Hossack et al., 1982</td>
<td>(43)</td>
<td>17 M+F normotensives</td>
<td>Treadmill</td>
<td>$8.9 \pm 15/-14.2 \pm 9.4$</td>
</tr>
<tr>
<td>Rasmussen et al.,</td>
<td>(44)</td>
<td>27 normals M+F</td>
<td>Ergometer</td>
<td>26/16 (no SD given)</td>
</tr>
<tr>
<td>1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gould et al., 1985</td>
<td>(21)</td>
<td>25 hypertensives</td>
<td>Ergometer</td>
<td>$-15 \pm 12/2 \pm 10$</td>
</tr>
<tr>
<td>Kaijser, 1987</td>
<td>(45)</td>
<td>15 normal subjects M+F</td>
<td>Ergometer</td>
<td>No absolute figures given but no significant difference for systolic BP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 12 subjects K-sounds did not disappear on auscultation</td>
</tr>
<tr>
<td>Turjanmaa et al.,</td>
<td>(46)</td>
<td>24 normal subjects</td>
<td>Ergometer</td>
<td>$13 \pm 18/18 \pm 13$</td>
</tr>
<tr>
<td>1988</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson et al., 1988</td>
<td>(15)</td>
<td>22 M+F normotensives</td>
<td>Ergometer</td>
<td>Percentage difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$3.5%$/$5.8%$ K-I/IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$16.6%$ K-V</td>
</tr>
<tr>
<td>Machine</td>
<td>Subjects</td>
<td>Exercise</td>
<td>Differences (SBP/DBP)</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------</td>
<td>----------</td>
<td>-------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Critikon 1165 (K-sounds + ECG gating)</td>
<td>19 normals</td>
<td>Treadmill</td>
<td>$1.5 \pm 19/ -4.9 \pm 8$</td>
<td>Hossack et al. 1982 (43)</td>
</tr>
<tr>
<td>Spacelabs 90202 (Oscilometry)</td>
<td>10 hypertensives</td>
<td>Ergometer</td>
<td>Incapable of measurement</td>
<td>White et al. 1990 (48)</td>
</tr>
<tr>
<td>Accutracker II (K-sounds + ECG gating)</td>
<td>12 hypertensives</td>
<td>Ergometer</td>
<td>$-1.7 \pm 8.9/1.3 \pm 6.1$</td>
<td>White et al. 1989 (49)</td>
</tr>
<tr>
<td>Colin ABPM 630 (K-sounds or oscillometry)</td>
<td>9 hypertensives</td>
<td>Ergometer</td>
<td>$-2.3 \pm 8.1/-2.6 \pm 11.5$ (K-sounds) $5 \pm 13.4/-3.6 \pm 7.4$ (oscillometry)</td>
<td>White et al. 1988 (50)</td>
</tr>
<tr>
<td>Del Mar Pressometer IV (K-sounds + ECG gating)</td>
<td>10 hypertensives</td>
<td>Ergometer</td>
<td>Absolute data not given See Fig. 2, poor reproducibility</td>
<td>White et al. 1990 (48)</td>
</tr>
</tbody>
</table>
Microphone detection of Korotkov sounds

There are currently at least 10 non-invasive ambulatory blood pressure monitors available (47) and those that have been tested in the exercise setting against the intra-arterial monitoring of blood pressure can be seen in Table 2. Bicycle ergometry is the commonest form of exercise used for the comparisons although treadmill testing and isotonic testing with hand-grip have also been employed (43, 48). For all published comparisons the number of individuals studied is extremely small when it is recalled that the number of individuals recommended for static validation of ambulatory monitors is 85 (51). Reference to Table 2 also shows that both oscillometry and detection of Korotkov sounds have been used by different monitors. Some that utilize a microphone have the facility for ECG gating such that the monitor will only detect sounds that follow within a precise interval of a QRS complex. Again, this should improve the accuracy and indeed in the one study where purported to compare several monitors (48) the Accutrack II using ECG-gating appeared to be the most accurate (Figs. 1 and 2). Even then, however, this ‘accuracy’ was probably not good enough to rely on this monitor in the exercise setting (Fig. 3).

Oscillometry

The Spacelabs 90202 monitor which detects blood pressure exclusively by the technique of oscillometry appears incapable of recording blood pressure during vigorous exercise (48). In his comparative paper in 1990 White (48) recommended that none

![Graph showing comparison of blood pressure monitors](image)

Fig. 1. A comparison of 4 different non-invasive ambulatory blood pressure monitors against a clinician auscultatory blood pressure during isometric exercise. Reproduced from White et al. (48) with kind permission of the authors and the editor of American Journal of Cardiology.
Fig. 2. A comparison of 4 different non-invasive ambulatory blood pressure monitors against a clinician auscultatory blood pressure during bicycle exercise. Reproduced from White et al. (48) with kind permission of the authors and the editor of American Journal of Cardiology.

Fig. 3. Standard plot to show the scatter of differences between intra-arterial blood pressure and that measured using an Accutrack II during different forms of exercise. Reproduced from White et al. (49) by kind permission of the authors and the editor of Journal of Hypertension.
of the available monitors was sufficiently accurate for proper assessment of blood pressure during exercise.

Several of the authors already quoted also compared conventional mercury sphygmomanometer measurements with those of an ambulatory blood pressure monitor. Both Garcia-Gregory and colleagues (39) and Radaelli and colleagues (52) have suggested that random variation may be greater with ambulatory monitors than with a technician measuring blood pressure with a mercury manometer.

For those interested in monitoring precisely blood pressure changes during exercise there appears to be no way around the fact that intra-arterial monitoring is the only accurate methodology. Recently, however, a study by Parati and colleagues (53) has raised the possibility that there is a form of indirect measurement which produces a close correlation with intra-arterial monitoring during exercise.

**Finger plethysmography**

It was nearly 20 years ago that Peñáz described a method of measuring blood pressure non-invasively by detecting changes in finger volume by plethysmography (54). This technology has now resulted in the ‘Finapres’ system which allows for a continuous measurement of blood pressure. Parati and colleagues (53) did not test dynamic exercise but during isotonic hand-grip or leg-raising, differences in both systolic and diastolic blood pressure between the Finapres system and intra-arterial measurements were small and of the order of 3 mmHg for systolic and between 0.5 and 1.2 mmHg for diastolic. More importantly the standard deviation of these differences was of the order of 2–3 mmHg for diastolic and 4 mmHg for systolic. These comparisons are closer than any of the others that have been discussed so far and thus we have a non-invasive methodology which allows continuous measurement of blood pressure and this may well be the best way forward for those interested in the cardiovascular physiology of exercise.

**IV. CLINICAL APPLICATIONS OF MEASUREMENT OF BLOOD PRESSURE DURING EXERCISE**

**Prediction of future hypertension**

Attempts have been made to relate the blood pressure response to exercise to the future development of hypertension. Franz (7) produced normative data during bicycle ergometry in 173 normotensive males and 150 normotensive females (age 20 – 50 years), indicating that a peak exercise blood pressure response should not exceed 200/100 mmHg. In a group of borderline hypertensive patients it was found that the pressor response to exercise was largely proportional to resting blood pressure, but approximately 50% of subjects had a frankly hypertensive response for the systolic blood pressure. These were termed ‘ergometer-positive’ and 97% of such subjects developed sustained hypertension over a 4-year follow-up period. Of the patients who were ‘ergometer-negative’ 32% developed sustained hypertension and thus the test as a whole had a sensitivity of 81% and a specificity of 94%. Dlin and colleagues (55) took two groups of normotensive individuals whose resting
blood pressure was < 140/90 mmHg and who were well matched for most demographic features. The only difference was that one group had been selected because of a bicycle ergometer exercise SBP > 200 mmHg compared with another group where exercise SBP was < 200 mmHg. Over a mean follow-up period of 5.8 years hypertension developed in 8 of the ergometer-positive groups but in none of the controls.

Similar predictive data have been obtained by Jackson and colleagues (56) and Wilson and Meyer (57).

Not all studies have been quite as successful in predicting subsequent blood pressure changes on the basis of exercise blood pressure (58). In the Muscatine Study 274 children were studied using a bicycle ergometer test. Resting systolic blood pressure was a better predictor than exercise blood pressure of long-term blood pressure changes. Hansen and colleagues (59) studied 132 children from a total group of over 1000 and found that exercise (bicycle ergometry) systolic blood pressure was not as good as the resting level as a predictor of future blood pressure.

It must be noted that all of these studies have used simple auscultatory methods of measuring blood pressure as an end-point, but most have relied on the more precise assessment of the systolic value.

Recently, Chaney and Eyman (60) performed similar studies in 100 male subjects with blood pressures < 140/90 mmHg. In this study treadmill exercise and hand-grip isometric exercise were studied and patients followed for 14 years. During that time 16 subjects became hypertensive and the best predictor of future of hypertension was the resting diastolic blood pressure closely followed by both the hand-grip and treadmill diastolic blood pressure. This study raises the question as to whether the simpler isometric testing might replace more complicated dynamic testing as a predictive tool and in studies by Cantor and colleagues (4) this would appear to be the case. Looking at 150 subjects and comparing isometric hand-grip with a Bruce protocol treadmill test, there was a good degree of correlation if one took the treadmill response as the standard. The predictive value of an abnormal isometric test was 90% with a sensitivity of 98% and specificity of 78%. Clearly if one were to consider such testing as a routine assessment of borderline patients, the simpler test would be preferable.

As can be seen in Chapter 12, 24-hour ambulatory blood pressure may give a good guide to the presence or absence of sustained hypertension and, in at least two studies (61, 62) a good correlation was found between laboratory exercise testing and 24-hour ambulatory blood pressure.

Finally, Molyneux and Steptoe have shown that normotensive adolescents with a family history of hypertension have an exaggerated blood pressure response to submaximal exercise in comparison to adolescents without the family history (63).

**Prognostic indicator in hypertension**

There are no studies relating exercise blood pressure in hypertensive subjects to ultimate morbidity or mortality. There is however an increasing body of information to suggest that exercise blood pressure relates very closely to the degree of left ventricular hypertrophy which is in itself a powerful predictor of mortality (64–66).

It seems fairly clear that echocardiographic assessment of left ventricular size
relates more closely to exercise blood pressure than to resting blood pressure (67–72). Ren and colleagues (67) studied 67 hypertensive individuals during treadmill exercise measuring blood pressure by the auscultatory method. The correlation between exercise systolic blood pressure and left ventricular mass was good ($r = 0.58$) and all individuals whose systolic blood pressure exceeded 190 mmHg during exercise had increased left ventricular mass by echocardiography. A similar relationship was found by Nathwani and colleagues (68) in 20 young mildly hypertensive subjects where the relationship between submaximal treadmill exercise and left ventricular mass was 0.57. Using an electronic automated measurement of blood pressure in 16 untreated hypertensives, Ferrara and colleagues (69) demonstrate an $r$-value of 0.52 for exercise systolic blood pressure and left ventricular mass, whereas the $r$-value for resting blood pressure was only 0.2. Giaconi and colleagues (70) studied 18 patients with borderline hypertension without evidence of left ventricular hypertrophy on echocardiography. This study showed that the relationships between casual diastolic blood pressure or systolic blood pressure response to exercise and left ventricular mass were similar ($r = 0.53$ and 0.55, respectively). Most recently Gottdiener and colleagues (71) studied 39 normotensive males during treadmill exercise. The peak SBP response to exercise was $> 210$ mmHg in 22 and less in 14. Left ventricular hypertrophy was found in 14 of the 22 with excessive SBP response and only 1 of the group with a 'normal' response (Fig. 4). This study and an accompanying editorial (72) clearly outlined the close relationship ($r = 0.65$) between left ventricular mass and blood pressure response to exercise (Fig. 5).

**Fig. 4.** Echocardiographic left heart wall and chamber dimensions in those subjects (closed circles) who achieved a peak systolic blood pressure with maximal exercise $> 210$ mmHg in comparison with those controls (open circles) who did not. Circles and half brackets indicate means and standard deviations respectively. Reproduced from Gottdiener et al. (71) with kind permission of the authors and the editor of the *Annals of Internal Medicine.*
Fig. 5. Relation of left ventricular mass index to maximum systolic blood pressure achieved with exercise. The vertical broken line represents the dividing line for left ventricular hypertrophy, the horizontal broken line for the peak normal maximal systolic response to exercise. Reproduced from Gottdiener et al. (71) with kind permission of the authors and the editor of the Annals of Internal Medicine.

These studies extend earlier observations which indicate that ambulatory blood pressure is a better determinant of left ventricular size than resting blood pressure (73, 74).

The simplistic explanation of such data is that, irrespective of resting blood pressure levels, recurrent stresses throughout the 24-hour period are likely to induce cardiac hypertrophy and thus dictate ultimate outcome. The intriguing possibility that the left ventricular hypertrophy might come first, generating an excessive cardiac output in response to exercise and hence a bigger blood pressure rise, was raised by Devereux (72) and is clearly worthy of further study.

Assessment of antihypertensive therapy

All treatment trials of hypertension which have assessed outcome have monitored resting blood pressure. If, however, ambulatory or in particular exercise blood pressure represents a better indicator of outcome, it would be important to assess the effect of antihypertensive drugs on the response of blood pressure to exercise. On theoretical grounds, for example, a non-selective $\beta$-adrenoreceptor blocker might be expected to result in an increased pressor response to exercise due to the unopposed alpha-activity consequent upon sympathetic discharge (see Ref. 75). Some authors have been unable to demonstrate an affect of propranolol in reducing exercise-induced systolic increases (76), whereas others have found beta-blockers to be as effective as (whether cardioselective or non-selective) (77) or even better than
diuretics (78) or clonidine (79, 80). A small comparative study of hydrochlorothiazide, guanethidine, reserpine and hydralazine indicated no ability of these drugs to prevent a systolic blood pressure rise following exercise (81) and even the newer angiotensin-converting-enzyme inhibitors, captopril (82), enalapril (80) and cilazapril (83), seemed relatively ineffective in preventing the systolic increases following exercise.

Whether these findings are relevant to cardiovascular outcome is uncertain and in all studies the numbers of individuals involved are small.

Assessment of patients with cardiac disease

The commonest indication for exercise testing in cardiovascular medicine is in the diagnosis or prognosis of ischemic heart disease. Measurement of blood pressure has been a standard part of such testing usually involving simple auscultatory measurement. There is good evidence that the blood pressure response to stress is a predictor of ultimate mortality (27, 84 – 86). The presence of pre-existing coronary artery disease reduces the blood pressure response to exercise (14, 27) and the lower the SBP response to exercise, the poorer the ultimate prognosis (85). An exaggerated rise in diastolic blood pressure (with all the caveats with regard to accuracy) has also been suggested as a predictor of the presence of coronary artery disease and mortality (87).

V. CONCLUSIONS

The cardiovascular physiological responses to exercise are well delineated and have been best described using intra-arterial techniques for blood pressure monitoring. With the possible exception of finger plethysmography, all forms of indirect measurement of blood pressure are prone to significant random errors during exercise and this is particularly so for the estimation of diastolic blood pressure. Non-invasive monitoring is probably more accurate if exercise is submaximal and inaccuracies are undoubtedly related to movement of the arm. Static or isotonic exercise (e.g. hand-grip testing) is less prone to error in measurement than the more vigorous dynamic or isometric testing (treadmill or bicycle ergometry). There is evidence to suggest that static tests may give similar information to dynamic testing and could therefore replace the latter if the blood pressure response to exercise is the required parameter.

Despite the observations in various treatment trials of hypertension there is increasing evidence that morbidity and mortality in hypertensive patients may be more closely related to ambulatory pressures than those recorded in the clinic (88) and we have reviewed evidence to suggest that exercise-induced rises in blood pressure may be even more important in determining outcome. Despite the major inaccuracies outlined in non-invasive monitoring of blood pressure during exercise it is precisely with these simple techniques that diagnostic and prognostic values have been attained and, provided that measurements are made of the systolic pressure only, meaningful clinical information can be obtained non-invasively.

There is a need to improve the ability to measure blood pressure during exercise.
without intra-arterial invasion and such developments are necessary for more detailed studies in this area.

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10. Measurement of blood pressure in epidemiological surveys

I.J. Perry and D.G. Beevers

Epidemiological research is of basic importance to our understanding of the distribution and the determinants of blood pressure in populations, as well as our knowledge of the prognostic significance of specific blood pressure readings in individuals. Research in epidemiology is fundamentally an exercise in measurement, where the primary objective is to minimize measurement error when applying relatively simple tests to large populations. The subject of measurement and measurement error is therefore of major importance.

The measurement of blood pressure in epidemiological surveys depends on the development of standardized measurement techniques. The technique employed must be capable of detecting changes and differences within and between populations which would be trivial at the individual level. For instance, differences in mean blood pressure of as little as 2 mmHg may be of immense significance at the population level. This is because a relatively minor shift in mean population blood pressure has a disproportionate effect on the number of individuals in the upper tail of the blood pressure distribution. Any technique adopted, therefore, should satisfy a number of basic requirements. It must be valid, i.e. it should measure blood pressure accurately when compared with a standard technique free of systematic error or bias. It should have an acceptable level of precision or repeatability, i.e. the technique of measurement and the conditions of measurement should be such as to minimize random biological variability and random error in measurement. The technique needs to be convenient and practical and capable of being communicated to relatively large numbers of field workers, including medical, nursing and paramedical staff.

I. TRAINING

Detailed instructions on the use of the standardized technique should be supplemented by regular training and retraining of observers, regardless of how senior or apparently reliable. This training may be based both on standard material such as London School of Hygiene audio-tapes (1) or the British Hypertension Society audio-visual tapes (2) and the assessment of investigators using double-headed
stethoscopes. Training should be accompanied by formal measurement of within-
observer and between-observer variation to demonstrate the magnitude of observer
error. This latter exercise should continue throughout the study to maintain atten-
tion to the details of the measurement technique, to provide data for quality control
and to allow adjustment if necessary for reliability in the analysis.

The major sources of variability and error in blood pressure measurement are
summarized in Table 1. Recommendations on the methodology and standardization
of blood pressure measurement techniques have been published which take account
of sources of variability and of the basic requirements of a blood pressure measure-
ment technique as discussed above (3 – 6). Cardiovascular Survey Methods (3) is a
definitive monograph which provides detailed recommendations on the methods
and standardization of indirect blood pressure measurement in epidemiological
surveys as well as a discussion of principles of measurement. The manual of opera-
tions for the INTERSALT study (7), an international co-operative study on the rela-
tion of sodium and potassium to blood pressure, has also been published (8) and
is a further valuable reference source in this area.

Of equal importance to good blood pressure measurement technique in popula-
tion surveys is the careful measurement and recording of personal and environmen-
tal factors which influence blood pressure such as age, sex, body mass index, ethnic
origin, medications and other variables which may confound the relationship be-
tween blood pressure and the factor(s) of interest. The list of confounding factors
will obviously vary with the study hypothesis. Attention to the details of the blood
pressure measurement technique, however, will not compensate for error or mis-
classification in the measurement of confounding factors.

II. VALIDITY

The validity of a blood pressure measurement technique depends on the accuracy
of the measuring device used and the avoidance of systematic error or bias in recor-

TABLE 1. Sources of blood pressure variability and measurement error*

<table>
<thead>
<tr>
<th>Within-subject variation</th>
<th>Observer/Instrument variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress/Emotion</td>
<td>Cuff size relative to arm</td>
</tr>
<tr>
<td>Posture/Arm position</td>
<td>Inflation/deflation rate</td>
</tr>
<tr>
<td>Exertion</td>
<td>Instrument calibration</td>
</tr>
<tr>
<td>Diurnal variation</td>
<td>Observer – subject interaction</td>
</tr>
<tr>
<td>Air temperature</td>
<td>Observer bias</td>
</tr>
<tr>
<td>Smoking</td>
<td>Observer fatigue</td>
</tr>
<tr>
<td>Recent meal</td>
<td>Digit preference</td>
</tr>
<tr>
<td>Full bladder</td>
<td>End-point definition</td>
</tr>
<tr>
<td>Season</td>
<td>Hearing threshold</td>
</tr>
<tr>
<td>Arrhythmia (e.g. atrial fibrillation)</td>
<td></td>
</tr>
</tbody>
</table>

* List not exhaustive. Observer/Instrument variation includes within- and between-
instrument and within- and between-observer variation.
ding the pressure. Assessment of the accuracy of blood pressure measurement devices is difficult. Blood pressure may be measured by a direct intra-arterial catheter, by indirect oscillometric or by indirect auscultatory and palpatory methods. Direct and indirect techniques of measurement of blood pressure cannot be compared directly. Indirect techniques measure the external pressure in the constricting cuff at which the arterial blood commences to flow (systolic pressure) and the pressure at which flow is completely restored (diastolic pressure). These pressures are determined by a number of other factors in addition to the actual intra-arterial pressure and are particularly influenced by the size of the arm and the size of the cuff. Intra-arterial blood pressures are lower than indirect measurements and while they may be physiologically more valid, they have not as yet been assessed in long-term epidemiological or prognostic studies. Furthermore, the procedure of arterial catheterization is not without hazard and is largely confined to highly specialized research centers. For practical purposes, therefore, we must regard the indirect auscultatory method as the standard in epidemiological research as current epidemiological data are based almost entirely on this method.

The methods for assessing agreement between the many indirect blood pressure measurement techniques and devices has been beset by problems associated with the unique lability of blood pressure recordings. Agreement on procedures to overcome these problems has been poor (9), and statistical analysis of agreement between devices has been dominated by correlation and regression, techniques we now know to be inadequate for this purpose (10). Essentially correlation measures the strength of the linear relationship between measurements provided by the standard and test device and regression examines the form of the relationship — neither technique measures agreement between the devices (10). Recommendations on standard methods for the comparison of blood pressure measurement techniques and devices have been proposed, that address many of these issues (11).

A wide range of automated (self-inflating) or semi-automated (manual inflation) indirect blood pressure measuring devices are currently available, and some have been successfully used in epidemiological surveys (12). Ambulatory blood pressure monitoring is increasingly used in the clinical assessment and management of hypertensive patients (13) and there is now a need for epidemiological surveys using ambulatory blood pressure recordings to place the large amount of mainly clinical data in a population context. If one proposes to use an automated blood pressure measurement device, it is absolutely essential to ensure that the equipment used reaches acceptable standards of accuracy as compared with the mercury sphygmomanometer, and also to ensure that it remains accurate under field conditions and is safe and convenient (11, 14, 15).

**Observer bias and digit preference**

Observer bias and terminal digit preference are major sources of systematic error in the measurement of blood pressure in epidemiological surveys. The London School of Hygiene (LSH) sphygmomanometer developed by Rose and colleagues in 1964 (16) addressed these problems as well as the issue of variable cuff inflation and deflation rates. This apparatus, although somewhat cumbersome and complex, was
widely used and for many years was the standard for indirect blood pressure measurement. The Hawksley random-zero or 'zero-muddler' sphygmomanometer (17) was developed as a simpler instrument, which, although not controlling inflation and deflation pressures, does reduce observer bias and terminal digit preference. It operates on the principle that if the observer is blinded to the zero level before each recording, the measurement will not be influenced by prior knowledge of, or anticipation of, the subject's blood pressure. Furthermore, the need to subtract the random-zero level from the observed blood pressure level discourages rounding towards the nearest terminal digit. There is good evidence from large epidemiological surveys, using large numbers of observers, that these objectives are achieved using the Hawksley random-zero sphygmomanometer (18).

In 1982 Fitzgerald and co-workers described a calibration error in the LSH sphygmomanometer compared with a standard mercury manometer and further demonstrated that the LSH device is associated with a systematic interpretive underestimation of blood pressure when compared with the Hawksley random-zero sphygmomanometer (19). This paper, although provoking correspondence in defence of the LSH device (20, 21), has been influential in determining the current pre-eminence of the Hawksley random-zero sphygmomanometer in epidemiological research. This is not to say, however, that the Hawksley device can be assumed to be entirely free of systematic error. It has been shown to underestimate blood pressure when compared with the standard mercury sphygmomanometer (22), probably due to a negative correlation between the zero level and the corrected blood pressure, i.e. higher zero levels tend to be associated with lower recorded pressures (23). The likely explanation for this association is failure of the observer to inflate the cuff to the level recommended by the manufacturers (200 mmHg, a level not infrequently associated with discomfort) before beginning the blood pressure reading.

To allow for assessment of this potential bias in the analysis, the random-zero level should be routinely coded with the corrected blood pressure readings.

End-point definition

The definition of diastolic end-points, whether muffling or disappearance of sounds, corresponding with the onset of the fourth or fifth phase of Korotkov sounds is a further potential source of systematic inter-observer variation. The current consensus, following several decades of conflicting recommendations (24 – 27), favors the use of the fifth phase of Korotkov sounds for the measurement of blood pressure in adults, with fourth-phase Korotkov sounds given preference when measuring blood pressure during pregnancy, in children, adolescents and in exercising subjects (6). As one would anticipate given the subjective nature of 'muffling', there is considerable inter-observer variation in the detection of fourth-phase Korotkov sounds. Hense and colleagues reviewed the distribution of the measured gap between the fourth- and fifth-phase diastolic pressure in over 2000 adults, whose blood pressure was measured by 13 highly trained observers (28). Non-detection of fourth phase (muffling of Korotkov sounds) ranged from 10% to 79% between the observers. There is no reason to suppose that agreement of fourth-phase Korotkov sounds is appreciably better when measuring blood pressure in children, pregnant women or exercising subjects and we would argue that the case
for retaining fourth-phase Korotkov sounds in these circumstances should be reviewed.

**Cuff size**

Cuff size, and particularly the overestimation of blood pressure in subjects with obese arms, is a further important source of systematic error in measurement (29, 30). The American Heart Association and the World Health Organisation have issued diverse recommendations on the appropriate cuff size for indirect measurement of blood pressure (24–26, 31). Both the length and the width of the inflatable bladder inside the cuff are important. However, a bladder that is large relative to the size of the arm is associated with less error than one that is small. The British Hypertension Society currently recommends that the length of the bladder should be at least 80% of the circumference of the arm and the width of the bladder should be at least 40% of the arm circumference (5). For normal or lean arms a $35 \times 12$ cm bladder is now recommended, as opposed to the $23 \times 12$ cm bladder usually supplied. For obese arms (circumference greater than 33 cm) a ‘large adult’ cuff with a $42 \times 15$ cm bladder is recommended. Population-based data on the prevalence of ‘obese arms’ is limited. Data from a small study which we have reported is reproduced in Table 2 (32). In children over the age of 5 years a $12 \times 8$ cm bladder is recommended.

The maintenance and periodic recalibration of blood pressure measurement devices over the duration of the survey is important and should be specifically allowed for in the study design. Aneroid sphygmomanometers are more likely than mercury sphygmomanometers to develop mechanical faults leading to inaccurate

<table>
<thead>
<tr>
<th>TABLE 2. The frequency of arm circumference of more than 33 cm in a population (Birmingham Factory Screening Project) and a clinical (blood pressure clinic) setting (32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers studied</td>
</tr>
<tr>
<td>Population survey (210)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>BP clinic (209)</td>
</tr>
<tr>
<td>White men</td>
</tr>
<tr>
<td>White women</td>
</tr>
<tr>
<td>Black men</td>
</tr>
<tr>
<td>Black women</td>
</tr>
<tr>
<td>Asian men</td>
</tr>
<tr>
<td>Asian women</td>
</tr>
<tr>
<td>All</td>
</tr>
</tbody>
</table>
measurement (33) and therefore are best not used in large-scale epidemiological surveys.

**Subject—observer interaction**

Whereas many sources of bias in blood pressure measurement, such as those associated with diurnal variation (34), the position of the subject and his upper arm in relation to the heart (35), changes in air temperature (36) and season (37) are readily quantified and may be reduced by standardization, the largest source of inter-observer bias — that associated with the interaction between the subject and observer — is the most difficult to control. In a clinical setting, for instance, an increase in blood pressure averaging 27 mmHg systolic and 15 mmHg diastolic is described, associated with the arrival of a doctor at the bedside (38). The instructions on preparation for blood pressure measurement in the INTERSALT manual (8), which specify, for instance, the nature and content of the conversation between subject and observer prior to the blood pressure measurement, are an indication of the attention to detail required to overcome this problem.

Systematic errors are important as they distort calculations of the mean blood pressure in different populations under study as well as estimates of the effect of environmental factors on blood pressure and measures of the relative risk of cardiovascular disease associated with different levels of blood pressure. Systematic error is not reduced by increasing the size of the study sample and it is rarely possible to adjust for it in the analysis. Accordingly it must be detected and removed at the design or pilot-study stage of the survey.

**III. PRECISION**

Lack of precision or repeatability in measurement is due to random variation and error, which in the context of blood pressure measurement derives generally from within-observer, within-instrument and within-subject variability (see Table 1). Even under carefully standardized conditions of measurement, the within-subject standard deviation for both systolic and diastolic blood pressures is approximately half that of the between-subject standard deviation (39). It is influenced by age, race, sex, hypertensive status and cardiac arrhythmia such as atrial fibrillation (18, 40). Random error is perceived to be less of a threat to the quality of study data than systematic error, on the basis that random errors generally ‘cancel each other out’, so-called non-differential misclassification. However, random error does reduce the precision of estimates such as means and relative risk, i.e. it increases the standard error and reduces study power. Furthermore, the strength of observed associations is diluted towards a zero effect. Precision and study power are restored by replication of measurements and by increasing sample size, but at a cost to the efficiency or even feasibility of a study. The tendency for random error to dilute etiological associations towards the null effect is not reduced by increasing sample size but only by increasing the number of replicate measurements.
Regression to the mean

The phenomenon of regression to the mean, i.e. the tendency for initially high blood pressure values to fall with repeated observation, is a familiar consequence of random variation. It is accentuated by the familiarization of the examinees with the measurement technique and reduction of their initial ‘flight or fight’ reaction to the observer. Less marked and less widely appreciated, though it is an inevitable consequence of the same phenomenon of regression to the mean, is the tendency for initially low readings to rise on retesting (41). Regression to the mean, as with other forms of random error, dilutes or weakens etiological associations, such as the association between blood pressure levels and cardiovascular disease. This phenomenon, referred to rather obtusely as ‘regression dilution bias’, has been addressed in a recent meta-analysis of the relationship between blood pressure and vascular disease (42).

Reliability

The concept of reliability of measurement is of central importance in the analysis of blood pressure data in epidemiological surveys. Reliability refers to the degree of random error (within-subject/within-observer variability) compared with the variation between individuals in the particular population studied. A reliable measurement is one where random error is insignificant compared to the variation between individuals. Where reliability is low, epidemiological associations are obscured by random ‘noise’. For example, if one examined the relationship between sodium excretion and blood pressure using unreliable techniques, the measured random fluctuations in an individuals’ sodium excretion and blood pressure from day to day could be as large as the variation in these parameters between individuals in the population studied. Accordingly, any associations between sodium excretion and blood pressure would be obscured by random error or ‘noise’ in the data. Reliability (expressed as a proportion or as a percent) is study-specific and is readily derived, provided data on replicate measurements are available on a subset of subjects (43). The reliability of a measured variable may be subdivided into the precision of the measurement, i.e. freedom from measurement errors and the dependability of measurement, reflecting the variables’ freedom from short-term random fluctuations (43). Reliability is enhanced by increasing the number of replicate measurements. In large observational studies of blood pressure, however, little is gained by recording more than two measurements (18).

A measure of reliability allows for adjustment of the estimate of effect in the ultimate analysis. In the INTERSALT study, for instance, replicate blood pressure and 24-hour urinary sodium excretion measurements were obtained on a subset of individuals which allowed for the estimation of the reliability of these measurements and thereby for the partial adjustment of the blood pressure/24-hour sodium excretion regression coefficients (7). Unfortunately the methodology for adjusting for reliability in multiple regression analysis is not well understood and further developments are awaited with interest.

Epidemiology is primarily concerned with validity and precision in measurement whether the instrument of measurement is a questionnaire or a sphygmomanometer.
A clear conception of the issues involved in the measurement of exposure and disease provides a focus and a rigorous blueprint for the overall study design.

REFERENCES


11. Non-invasive ambulatory blood pressure measurement

Wolfgang A. Meyer-Sablek

As early as 1898, Hill (1) was able to register daily fluctuations and nocturnal decrease of blood pressure using indirect palpation with the aid of a sphygmograph. The variability of measurements of casual blood pressure has been discussed for decades in the literature (2–4). However, it took almost a century to develop automated ambulatory blood pressure measuring devices capable of monitoring blood pressure over 24 hours. This delay in development may be attributed firstly to failure to appreciate the clinical importance of blood pressure variations and variability, and secondly to the technical slowness of development of miniaturized and reliable monitors for routine daily use (5,6).

Blood pressure is a dynamic parameter subject to short-term (e.g. beat-to-beat) and long-term (e.g. biphasic diurnal) variations. These fluctuations are due to complex internal (e.g. circadian) physiological mechanisms and external stimuli (e.g. work) creating a diurnal profile of blood pressure (7–10). The theoretical importance of identifying diurnal variations of different physiological parameters (11–14) and the clinical coincidence of acute cardiovascular events have been the goal of numerous investigations (15–21) and retrospective analyses within the last decade. The incidence of myocardial infarction (22), sudden cardiac death (23, 24), transient myocardial ischemia (19, 25, 26) and stroke (27) is not evenly distributed throughout the day and night, with morning hours carrying a significantly higher risk. In addition, it has been suggested that seasonal effects on arterial blood pressure (28–31) may, at least in part, account for the reported (32, 33) higher mortality from ischemic heart disease and stroke.

The recent technical improvements have been based on experience and knowledge of 24-hour ECG-monitors. These portable devices have developed from heavy bulky monitors and the problems of telemetric methods or tape-driven devices have been overcome by the use of light, reliable monitors with a solid-state memory. Progress in the development of small auscultatory and oscillometric recorders for ambulatory measurement of blood pressure has fulfilled early hopes for the construction of small, portable, noiseless, reliable, fully automated devices for clinical research and practice (34–36).
I. METHODOLOGY

Three different methods for monitoring blood pressure over a period of at least 24 hours are in use (Table 1): Direct intra-arterial blood pressure may be measured via a minicatheter in the arteria brachialis or radialis permitting beat-to-beat analysis. Non-invasive (indirect) ambulatory blood pressure monitoring (ABPM) by means of fully automatic devices is available with portable recorders (Table 2) using intermittent auscultatory or oscillometric readings via a standardized cuff on the upper arm. Non-invasive continuous blood pressure monitoring, using mostly finger devices, among a number of other methodological approaches, is being developed.

**Intra-arterial monitoring — the Oxford System**

The use of intra-arterial (i.e. direct) blood pressure measurement with portable ambulatory monitors was first described by Bevan and colleagues (37) in 1966 and has been improved and used by numerous groups (38 – 42). The commonly used Oxford device is unlike radiotelemetric systems — it can store data on a solid memory. This method not only permits beat-to-beat analyses but also statistical assessment of the complete diurnal blood pressure profile on the basis of more than 100 000 measurements of systolic, diastolic blood pressure and heart rate over 24 hours. However, the use of this technique is limited to experienced research groups. The prolonged insertion of an intra-arterial minicatheter in the non-dominant arm carries the risk of bleeding, infection and nerve trauma, which mitigates against the use of this procedure in routine clinical practice (see Chapters 2 and 16).

**Non-invasive ambulatory blood pressure monitoring**

The safety of devices utilizing direct intra-arterial measurement (43) and the limited applicability of self blood pressure measurements have favored the development of non-invasive ambulatory blood pressure monitoring. These techniques have rapidly gained acceptance as as useful, potentially accurate procedure in the routine clinical

<table>
<thead>
<tr>
<th>TABLE 1. Methods of 24-hour ambulatory blood pressure monitoring (ABPM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive ABPM</strong></td>
</tr>
<tr>
<td>Direct continuous ('Oxford Method')</td>
</tr>
<tr>
<td>Intra-arterial brachial catheter in the brachial or radial</td>
</tr>
<tr>
<td>artery</td>
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<td></td>
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<tr>
<td></td>
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<td></td>
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</tbody>
</table>
### TABLE 2. Weight of monitors, methods of blood pressure recording, ECG gating/monitoring and validation requirements in direct ambulatory automatic 24-hour blood pressure devices

<table>
<thead>
<tr>
<th>Monitors (manufacturers)</th>
<th>Weight (g)</th>
<th>Weight Methods</th>
<th>ECG</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Auscultation</td>
<td>Oscil</td>
<td>R-wave</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>lome</td>
<td>Monitoring</td>
</tr>
<tr>
<td><strong>Indirect intermittent ABPM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL 90202 [90207]</td>
<td>480</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(SpaceLabs, U.S.A.)</td>
<td>[380]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physio-Port II</td>
<td>580</td>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>(Hellige, F.R.G.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accutracker II</td>
<td>480</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Suntechn, U.S.A.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ABPM 630</td>
<td>780</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>(Colin, Japan)</td>
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<td></td>
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<tr>
<td>Medilog</td>
<td>600</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>(Oxford, U.K.)</td>
<td></td>
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<tr>
<td>TM 2420</td>
<td>490</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>(A &amp; D instruments,</td>
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<tr>
<td>Japan)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressurometer IV</td>
<td>780</td>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>(Del Mar Avionics, U.S.A.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novacor (France)</td>
<td>720</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CH-Press (Disitronic,</td>
<td>580</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Switzerland)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Indirect continuous ABPM**

| Portapres (TMO,         | 1200       | Finger cuff    | -   | -        | -    | -   | u.i.|
| Netherlands)            |            |                |     |          |      |     |     |

AAMI = American Advanced Association for Medical Instrumentation U.S.A.;
PTB = Physikalisch-Technische Bundesanstalt, Berlin, F.R.G.;
BHS = Britisch Hypertension Society, U.K.;

a = accepted;
f = failed;
u.i. = under investigation.
management of hypertension (44, 45) and in the assessment of antihypertensive
drugs (46–48). Semi-automatic procedures (49, 50) require the patient to press a
button to trigger the measuring process or to inflate the cuff, thereby allowing
measurement only during the awake phase. Fully automatic devices are capable of
recording the blood pressure and pulse rate at pre-programmed intervals of
2–60 minutes with individual adjustment for day and night over 24- or even 48-
hour periods.

*Auscultation — ECG gating*

Most monitors for recording 24-hour ambulatory blood pressure determine blood
pressure by using standard auscultation of Korotkov sounds via one or two
microphones either taped over the brachial artery or sewn into the cuff.

The auscultatory technique may be affected by background noises (e.g. muscle
contraction, transmission of high-frequency bruit from machines or motor) which
may cause artefactual readings. In addition, the microphone may be sufficiently
sensitive to record Korotkov's sounds that are inaudible to the human ear, resulting
in systematic error, leading to low diastolic and high systolic pressure recordings
(51–53). Some devices are equipped with ECG leads to register Korotkov sounds
within the R-wave window. This requires application of 3 electrodes to the chest,
which restricts the patient and is therefore generally less tolerated than devices
without ECG electrodes. In addition, these electrodes do not prevent auscultatory
inaccuracy in patients with dysrhythmias (e.g. absolute or especially respiratory ar-
rhythmias). Some devices (e.g. Medilog ABP) use a two-pass process to measure
blood pressure by the microphonic detection of Korotkov sounds. The first pass oc-
curs during the cuff deflation itself. With ECG gating the processor picks out QRS
complexes and will not accept a sound from the transducer unless the time interval
from the QRS to the transducer sound is within a fixed time window of
100–500 milliseconds. The processor stores all the Korotkov sound data, with in-
formation on sound intensity, timing with respect to the ECG, cuff pressure, etc.
In the second pass, tests are applied to the stored data to identify and reject move-
ment artefacts. One of these tests makes use of a double microphone transducer.
The pulse travels down the brachial artery at a finite speed, so there is a measurable
delay from passing under the upper half (first microphone) to passing the lower half
(second microphone). If the delay between the sounds is not appropriate, that sound
will not be accepted. The processor also stores sound data to measure the delay time
from the QRS complex to sound; it then uses this to adjust the ECG gating in a more
selective manner for that individual patient.

*Oscillometry*

Oscillometric techniques have been used in the manufacture of small, light-weight
recorders, which may however require an expensive work station. Internal
algorithms are used to register waves generated by the brachial artery during cuff
deflation, the diastolic blood pressure being calculated via pre- and post-maximal
oscillations in an inflated, occluding upper arm cuff. This method (52, 56, 57) has
been criticised, because pulse pressure is influenced by cardiac output (e.g. cardiac
insufficiency), peripheral resistance (e.g. vasodilating drugs), and anatomical abnormalities of the artery (e.g. arteriosclerosis). Nevertheless, this procedure is now routinely used in the SpaceLabs devices (56–58) (Fig. 1) and the reliability has been shown to be at least as good for auscultatory devices. Oscillometric devices are moreover easier to handle and they are sufficiently robust to withstand the demands of ambulatory use.

*Techniques under investigation*

*Korotkov signal (K-II)* A new technique of indirect blood pressure measurement based on waveform analysis of the Korotkov signal (58, 59) which uses a specially designed transducer — a foil electric sensor — provides an accurate reading of both the low-frequency and high-frequency components of the signal. As cuff pressure is reduced, a high-frequency component of the signal develops, corresponding precisely to systolic pressure. The potential advantage of blood pressure measurement by the ‘K2 algorithm’ is that it can be done on the basis of pattern recognition rather than by an absolute level of sound, which varies greatly from one individual to another.

*Piezo foil* The piezo pulse meter has been utilized to measure pulse pressure. The applicability, accuracy and reliability of this technique is under investigation (60).

*Fig. 1.* Ambulatory patient with oscillometric monitor (SpaceLabs 90207).
Ultrasound  An ultrasound transmitter and receiver integrated into sphygmomanometer cuff and placed over the brachial artery have been used for ABPM. As the cuff is deflated, the movement of the arterial wall at systolic pressure causes a Doppler phase shift in the reflected ultrasound, and diastolic pressure is recorded as the point at which diminution of arterial motion occurs (61, 62). Another variation of this method detects the onset of blood flow at systolic pressure and has been found to be of particular value for measuring pressure in infants and children (63).

Pulse transit-time technique  The velocity of the pulse wave along an artery is proportional to the arterial pressure, and this principle has been used to evaluate changes of blood pressure by measuring changes of pulse wave velocity, by recording either the interval between the R-wave of the electrocardiogram and the radial pulses. Although the method has the advantage of not requiring a cuff and being theoretically suitable for beat-to-beat measurement of blood pressure, its accuracy has been found to be unacceptably low (64, 65).

Finger-cuff method of Peñáz  Arterial pulsation in a finger may be detected by a photoplethysmograph under a pressure cuff. The output of the plethysmograph is used to drive a servo-loop which rapidly changes the cuff pressure to keep the output constant, so that the artery is held in a partially opened state. The oscillations of pressure in the cuff are measured, and they have been found to resemble the intra-arterial pressure wave in most subjects. This method, first described by Peñáz (66)

Fig. 2. Ambulatory patient with the Portapres and two finger cuffs.
and subsequently developed (67), gives an accurate estimate of systolic and diastolic pressure, although both may be underestimated when compared to brachial artery pressures. This device, based on a one finger cuff (Finapres), which is now commercially available has been validated in several studies against intra-arterial pressures, mostly during anesthesia for surgical operations (68–72). A similar system (Portapres), using two finger cuffs (Fig. 2), has been described which provides beat-to-beat recording (Fig. 3) or a 64-second mean over 24 hours (Fig. 4).

**Energy source and pressurization**

Auscultatory and oscillometric devices may be powered by specially manufactured or commercially available rechargeable accumulators (nickel/cadmium batteries), but these power sources still present a problem. Although considerable improvements have been achieved, they may comprise up to 50% of the total weight of the portable recorder and may not be reliable. It is often difficult to determine precisely the point of time at which the accumulators have to be exchanged. Commercially available accumulators need to be changed after a maximum of twenty 24-hour profiles and this adds considerably to the cost and is also a source of environmental pollution. The utilization of a CO₂-cartridge for cuff pressurization decreases noise level (< 40 dB) and weight considerably, but allows only about 60 measurements over 24 hours.

An alternative to batteries are long-stroke or centrifugal pumps, but these are large and heavy and thus limit the development of lighter devices. It takes approximately 10 seconds to inflate the cuff until occlusion pressure is reached (generally 20 mmHg above the last systolic value). Cuff inflation does not, as frequently assumed, lead to alarm reactions with an increase in blood pressure (73). Some devices may announce the measurement process by a programmable alarm sound several seconds prior to inflation. Nevertheless, some patients do not like using these devices at work or in public. Another disadvantage is that the compression of the arm by the cuff and the pump noise may disturb sleep, making it impossible to assess nocturnal blood pressure variability.

![Finapres](image)

**Fig. 3.** Continuous finger pressure (upper trace) and constriction plethysmogram (lower trace) show pressure increases and simultaneous constriction reactions in adjacent fingers. Almost complete constriction is reached each time 3–4 seconds from the beginning. Return to a relaxed state takes slightly longer.
Data display, transfer and storage

Ambulatory recorders are usually equipped with segment liquid-crystal displays that can be programmed to announce each measurement process by an alarm signal, and display the data after each measurement cycle. Errors may be indicated in an encoded form (e.g. defective microphone) and can sometimes be corrected by the patient (e.g. position of the cuff) after advice from the laboratory.

Solid-state memory (operated by an 8-bit CMOS microprocessor or a similar device) stores the data (e.g. 32K RAM) until the batteries are empty. The data have to be transferred to a computer via an interface. The storage capacity of most devices is 300 measurement points per 24 – 48 hours of systolic, diastolic blood pressure and heart rate. Devices with a high storage capacity or with exchangeable energy sources and data storage units permit registration of two or more continuous 24-hour cycles. With the aid of an interface, the recorded data can be transferred to a computer for analysis and assessment. Manufacturers offer different assessment programs permitting editing of illogical data (e.g. systolic equal to diastolic pressure or pulse rates below 30 per min, etc.) Most manufacturers now offer computer software programs, which are compatible with many computer systems and it is no longer necessary to purchase a new computer system and monitor.

Fig. 4. Twenty-four-hour profile of systolic and diastolic blood pressure (mmHg) and heart rate using the finger cuff method (Portapres). 64-second-mean is provided, interruptions derive due to change of the two finger cuffs each 30 min. Reproduced with permission of T.H. Schmidt, 1990.
The availability of acoustic couplers, which have to be licensed in some countries (e.g. Germany), allow the transmission of data via telephone, thus permitting data from portable monitors to be transferred from peripheral centers to be stored, pooled and statistically analyzed in a central unit.

Side-effects

Side-effects associated with non-invasive ABPM are rare. In almost 3000 ABPM recordings, allergic exanthema and petechiae were observed in the area of the cuff in only 4 cases (74). Urticaria was caused either by the material (rubber) or detergent in the fabric cuff. Fixation of the microphone, electrodes or tubes caused plaster allergies in 6 cases. ABPM was refused by less than 10% of patients. Some patients do not accept it, because it attracts attention (noise, bulky monitors). Phlebitis of the arm vein has also been described (75) as a case-report on an old device. Sleep disturbances have been reported in up to 20% of patients (35).

Artifacts — effects of posture and activity

A reliable technical system is the first prerequisite for the reduction of artifacts. Energy failure may be responsible for artifacts and cable failures due to material fatigue may also occur. Sounds engendered by muscular contractions or external sounds at the place of work (e.g. engine noise or vibrations transmitted into the arm via a car steering wheel) can lead to unverifiable blood pressure values during ergometry (52, 76) and have to be taken into consideration during validation studies (34). Today most of the ABPM monitors give accurate blood pressure readings at rest, especially when the subject is seated and to a lesser extent when standing.

Accuracy is reasonably maintained in mild exercise and immediately after severe exercise, but ECG gating cannot secure accurate blood pressure readings during moderate to severe exercise. The evaluation of devices during sports activity has been limited (77). Provided the subject is seated or standing for the duration of recording, accuracy is maintained, even if the subject has recently stopped strenuous activity. There are few reports on the accuracy of ambulatory blood pressure recordings during exercise or simulated daily activities (78, 79) and most have shown similar inaccuracy during moderate to severe exercise. Guidelines for ambulatory recordings should include clear instructions to all subjects that the cuff arm must be held completely still once cuff inflation begins and for the duration of recording. The amount of activity being carried out may be simultaneously recorded by piezo-crystal-containing devices placed on the leg or arm.

Patient instruction and protocol

Detailed instruction to the patient leads to fewer artifacts (see below). Some devices repeat the measuring procedure after an inadequate reading so as to maintain the pre-programmed measuring times. Patients are asked to keep a 24-hour diary so as to provide additional information on physical activity, stress, working time and sleeping phase. The times of drug intake are also important in the evaluation of antihypertensive therapy. Precise positioning of the directional microphone is required
for the auscultatory procedure and removal of the cuff (e.g. taking a shower) can lead to incorrect measurements. Replacement of the cuff is easier with oscillometric than with Korotkov-sound-detecting monitors.

Reproducibility

Reproducibility of circadian blood pressure, a necessary prerequisite for all systems, has been confirmed by different investigators (80 – 82), although a certain adaptation cannot be excluded. Comparative re-measurements should, however, be performed under comparable daily routine conditions, especially in relation to work and activity. Profiles registered at the weekend should not be compared with diurnal profiles during the working week.

Accuracy

Many validation studies have been published comparing the accuracy of non-invasive recorders with either simultaneously determined auscultatory readings taken with a mercury column or intra-arterial readings (56, 57) Such studies (34) have included the Del Mar Avionics recorder (83 – 87), the SpaceLabs recorder (52, 53, 56, 57, 88, 89), the Accutracker (52, 90 – 92) and semi-automatic devices like the Remler (49, 50, 93). There is now a second generation of ambulatory recorders which includes the SpaceLabs 90202 (57), the Del Mar Avionics PIV, the A&D TM 2420 and the Oxford Medilog (34, 94, 95). As with all non-invasive methods, systolic pressure is more reliably recorded than diastolic pressure. There does not appear to be any systematic difference between the accuracy of recorders using Korotkov sound detection or oscillometry.

II. VALIDATION STANDARDS OF AMBULATORY BLOOD PRESSURE MONITORING

Validation requirements have not been standardized worldwide and 3 different national validation protocols are available. The American Association for the Advancement of Medical Instrumentation (AAMI) (96), the German Physikalische Bundesanstalt (PTB) (74) and the British Hypertension Society (BHS) (37) protocols are compared in Table 3. These standards are helpful in restricting acceptance of devices for ABPM. Validation studies are helpful also in guiding manufacturers to rectify reported difficulties in clinical performance and accuracy.

The AAMI protocol and the PTB standards, however, have been drawn up by manufacturers and engineers rather than by clinical investigators. The BHS protocol devised by clinicians is, so far, the most useful assessment as it specifically addresses issues such as observer training and variability, calibration and device variability, and clinical performance of the recorders during normal daily activities. A deficiency in the BHS standard is the absence of a validation test during motion. So far, none of the available devices has proven to be accurate during walking, running or ergometry (51, 79, 97). The method of comparing differences between measurement techniques has also been improved in the BHS guideline, as it relies on graphic and

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>AAMI</th>
<th>PTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>User's manual</td>
<td>required</td>
<td>required</td>
</tr>
<tr>
<td>2</td>
<td>Labeling</td>
<td>detailed req.</td>
<td>detailed req.</td>
</tr>
<tr>
<td>3</td>
<td>Stability</td>
<td>10 000 cycles</td>
<td>15 000 cycles</td>
</tr>
<tr>
<td>4</td>
<td>Battery check</td>
<td>required</td>
<td>required</td>
</tr>
<tr>
<td>5</td>
<td>Pressure replay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1</td>
<td>Accuracy</td>
<td>± 3 mmHg or</td>
<td>± 4 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 2%</td>
<td>(whole range)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>whatever is greater</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(range: 20 – 250 mmHg)</td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>Digit step</td>
<td>not specified</td>
<td>1 mmHg</td>
</tr>
<tr>
<td>6</td>
<td>Pneumatic system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1</td>
<td>Max. cuff pressure</td>
<td>330 mmHg</td>
<td>ca. 300 mmHg</td>
</tr>
<tr>
<td>6.2</td>
<td>Max. measuring time</td>
<td>5 min</td>
<td>not specified</td>
</tr>
<tr>
<td>6.3</td>
<td>Max. leakage</td>
<td>2 mmHg/min</td>
<td>4 mmHg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(at 300 mmHg, 500 cm³)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 cm³)</td>
<td></td>
</tr>
<tr>
<td>6.4</td>
<td>Cuff exhaust rate</td>
<td>1 – 20 mmHg/s</td>
<td>Korotkov method:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 – 3 mmHg/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>osc. method: 2 – 8 mmHg/s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>recommendations of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the German Hypertension League</td>
</tr>
<tr>
<td>6.5</td>
<td>Cuff size</td>
<td>Specified in AAMI SP9-1985</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Resistance to external influences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1</td>
<td>Storage temperature</td>
<td>–20°C to 50°C</td>
<td>not specified</td>
</tr>
<tr>
<td>7.2</td>
<td>Operating temperature</td>
<td>10°C to 40°C</td>
<td>15°C to 25°C ambulatory blood pressure monitors: 0°C to 40°C</td>
</tr>
<tr>
<td></td>
<td>Humidity</td>
<td>15 – 90%</td>
<td>not specified</td>
</tr>
<tr>
<td></td>
<td>Altitude</td>
<td>–170 m to 1700 m</td>
<td>not specified</td>
</tr>
<tr>
<td>7.3</td>
<td>Vibration/shock</td>
<td>detailed req.</td>
<td>not specified</td>
</tr>
<tr>
<td>7.4</td>
<td>Infl. via i/o-interface</td>
<td>not specified</td>
<td>detailed req.</td>
</tr>
<tr>
<td>7.5</td>
<td>Electromagn. compatibility</td>
<td>not specified</td>
<td>detailed req.</td>
</tr>
<tr>
<td>8</td>
<td>Electrical safety</td>
<td>detailed req.</td>
<td>not specified</td>
</tr>
<tr>
<td>9</td>
<td>Clinical trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1</td>
<td>Procedure</td>
<td>detailed req.</td>
<td>detailed req.</td>
</tr>
<tr>
<td>9.2</td>
<td>Overall system efficacy</td>
<td>± 5 mmHg</td>
<td>sys: ± 8 mmHg</td>
</tr>
<tr>
<td></td>
<td>Mean difference</td>
<td></td>
<td>dia: −8/+ 4 mmHg</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>8 mmHg</td>
<td>6 mmHg</td>
</tr>
</tbody>
</table>
statistical analysis of mean differences and confidence limits for the standard method and the ambulatory blood pressure recorder rather than the regression analysis as required in the AAMI protocol.

Requirements of the AAMI and PTB

A number of recommendations or standards for sphygmomanometers have been developed by international organizations recently, and national requirements exist in the following countries: Austria, Australia, Canada, China, France, Germany, United Kingdom, Hungary, Yugoslavia, Japan, Sweden, Switzerland and United States (74).

A summary of the requirements of the American National Standard ‘Electronic or Automated Sphygmomanometers’ (ANSI/AAMI SP 10, 1987) and the German ‘Requirements and test regulations of the Physikalisch-Technische Bundesanstalt for Non-invasive Blood Pressure Measuring Equipment’ (PTB-A 15.4, 1988) are given in Table 3. In contrast to the United States, the Federal Republic of Germany requires that sphygmomanometers are subject to state supervision based on the Law on Metrology and Verification, which includes design testing and pattern approval. In addition, each instrument is verified every 2 years by local verification offices. Although the American and German requirements have been developed independently of each other, the performance levels are similar.

Besides technical and handling tests, both protocols stress the importance of clinical trials. In the clinical trial the automated sphygmomanometer is compared with reference methods, such as auscultatory measurement on the same or different limb as the tested instrument. Also intra-arterial measurements may be used. There are detailed descriptions on the number of patients involved, their age, their blood pressure range, etc. Automated sphygmomanometers rarely have difficulty meeting the limits for the mean difference, probably because deviations here can be avoided by proper adjustment. A more difficult problem is the accuracy of single measurements, represented by the standard deviation of the comparative measuring series.

The recommendations for performance testing provide the outline protocol of a method to compare equipment either against intra-arterial or non-invasive auscultatory measurements with a standard mercury sphygmomanometer. The standard requires that two trained, blinded observers measure blood pressure simultaneously 3 times over a period of 10–30 minutes on each subject. Agreement between the observers must be greater than a 95% significance level. Mean difference and standard deviation of the difference between the observers and the instrument are calculated separately for systolic and diastolic pressures. The database requires at least 85 subjects, with a defined range of blood pressures, as measured by the clinicians.

The BHS protocol (97)

Since the AAMI standard was published, methods of statistical analyses in the evaluation of devices have also changed. Most notably, the correlation coefficient, once regarded as the basis of comparison for studies of one device against another,
has been largely abandoned because it may suggest close accuracy when there are, in fact, gross differences between the devices being compared (98, 99).

A Working Party of the BHS has recently developed recommendations (BHS protocol) for ambulatory systems. This protocol has endeavored to keep the procedures as simple as possible, but to fulfill clinical requirements. The testing procedure has been designed to ensure that expensive and time-consuming analysis is not performed on devices which do not meet certain basic accuracy criteria.

The BHS evaluation program consists of 6 phases (see Appendix V to this volume):

Phase I  Observer training and assessment
Phase II Before-use interdevice variability assessment
Phase III In-use (field) assessment
Phase IV After-use interdevice variability assessment
Phase V  Device validation
Phase VI  Report of evaluation

Manufacturers cannot be obliged to guarantee the accuracy of their product, but it is likely that the legislative harmonization being prepared by the commission of the European Communities (CEN) with regard to essential safety requirements of medical devices will be extended to other aspects of device performance (100).

III. GUIDELINES FOR CLINICAL USE

More than a dozen commercially ABPM systems are available and the advantages and disadvantages are listed in Table 4.

At present, ambulatory monitors may be marketed after fulfilling local authority regulations, which are more concerned with safety than accuracy. However, the definition of reliability and precision of ABPM monitors is currently being debated and has led to the formation of committees to develop guidelines for the clinical evaluation of the recorders.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple (&gt; 60) blood pressure measurements per 24 hours</td>
<td>Disturbance of sleep or work with noisy cuff inflation</td>
</tr>
<tr>
<td>Evaluation of long-term (e.g. diurnal) variability</td>
<td>Limited normal data and treatment guidelines</td>
</tr>
<tr>
<td>Blood pressure during (usual) daily activity, blood pressure recording during sleep</td>
<td>Cost, calibration and validation</td>
</tr>
<tr>
<td>Exclusion of 'white coat hypertension'</td>
<td>Preselection of patients</td>
</tr>
<tr>
<td>No alerting response</td>
<td>No unrestricted use (e.g. during movements</td>
</tr>
<tr>
<td>No placebo effect</td>
<td></td>
</tr>
<tr>
<td>Reduction of treatment in mild hypertension (&gt; 25%)</td>
<td></td>
</tr>
</tbody>
</table>
The Berlin Consensus Document (101)

According to the statement of the Berlin Consensus Document based on the First International Consensus Conference on ABPM, the following factors must be taken into consideration in ambulatory systems for either research or clinical work:

1. Accuracy and reliability (proven by national authorities, e.g. AAMI, BHS, PTB)
2. Patient/user acceptability (especially weight, noise, ECG)
3. Computer compatibility including ability to transfer electronically (e.g. via telephone, disc)
4. Costs

Statistical analysis

Blood pressure monitoring over a short day or night-time cannot predict 24-hour average blood pressure (102, 103). Based on simultaneous continuous intra-arterial versus intermittent blood pressure measurements (104) and experience from clinical work, a 24 hour period should be divided as follows:

day-time 7.00 a.m. to 10.00 p.m. ± 2 h
night-time 10.00 p.m. to 7.00 a.m. ± 2 h

Intervals of recording should be:

day-time 15 – 30 min
night-time 30 min

For research the periods and frequency of recording may have to be altered to suit the project. A diary of daily activities (e.g. time at work, no sleep phase) should be completed.

Different methods of analysis are being assessed (100–114) but ABPM systems should at least provide the following:

Total number of readings
Missing and error readings
Mean and median daytime pressure
Mean and median night-time pressure
Mean and median 24-hour pressure

For research and assessment of antihypertensive drug effect the irregularity of measurement, the instability of the signal itself and device artefacts (< 5%) must be considered. A ‘smoothing procedure’ is therefore recommended. The standard procedure is staircase smoothing (often available in the commercial software programs) using hourly or bi-hourly averaging (arithmetic means) (Fig. 5). Robust measures such as median values are preferred. The Cosinor approach to data evaluation seems to be too rigid to give an appropriate summary of the data
Fig. 5. Hourly medians (24th, 75th percentile) for systolic, diastolic blood pressure and heart rate before (placebo, □) and after administration of carvedilol b.i.d. (〓) for 1 year (149).
(29, 30). A flexible approach is provided by spline-models, but they are more costly from the computational point of view (105, 112).

Normal values

Cardiovascular morbidity and mortality have been shown to be related to casual blood pressure. A basic deficiency in ABPM has been the lack of similar data. ABPM data have been published from selected and, usually, small groups preselected on the basis of normotensive blood pressure values on conventional

![24-HOUR ABP Diagram](image)

**Fig. 6.** Normal ABPM values from literature. The ambulatory pressure over 24 hours in various studies. For each study the mean with 95% confidence interval is presented in the top panels. The mean ± 3 standard deviations are given in the lower panels. Abbreviations are used to indicate the technique of recording: IA = intra-arterial; A = auscultatory; A(O) = auscultatory with oscillometric back-up; and O = oscillometric. From Staessen et al. (115).
<table>
<thead>
<tr>
<th>Age range (yr)</th>
<th>Men</th>
<th>30-39</th>
<th>40-49</th>
<th>50-79</th>
<th>All</th>
<th>30-39</th>
<th>40-49</th>
<th>50-79</th>
<th>All</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-29</td>
<td>121 ± 12</td>
<td>122 ± 11</td>
<td>125 ± 16</td>
<td>133 ± 15</td>
<td>124 ± 14</td>
<td>110 ± 11</td>
<td>113 ± 10</td>
<td>121 ± 17</td>
<td>130 ± 24</td>
<td>115 ± 15</td>
</tr>
<tr>
<td>30-39</td>
<td>125 ± 16</td>
<td>133 ± 15</td>
<td>124 ± 14</td>
<td>110 ± 11</td>
<td>113 ± 10</td>
<td>121 ± 17</td>
<td>130 ± 24</td>
<td>115 ± 15</td>
<td>119 ± 15</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>133 ± 15</td>
<td>124 ± 14</td>
<td>110 ± 11</td>
<td>113 ± 10</td>
<td>121 ± 17</td>
<td>130 ± 24</td>
<td>115 ± 15</td>
<td>119 ± 15</td>
<td></td>
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<tr>
<td>50-79</td>
<td>121 ± 17</td>
<td>130 ± 24</td>
<td>115 ± 15</td>
<td>119 ± 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-29</td>
<td>73 ± 9</td>
<td>77 ± 8</td>
<td>86 ± 10</td>
<td>81 ± 11</td>
<td>78 ± 10</td>
<td>71 ± 8</td>
<td>73 ± 8</td>
<td>78 ± 9</td>
<td>81 ± 12</td>
<td>73 ± 9</td>
</tr>
<tr>
<td>30-39</td>
<td>77 ± 8</td>
<td>86 ± 10</td>
<td>81 ± 11</td>
<td>78 ± 10</td>
<td>71 ± 8</td>
<td>73 ± 8</td>
<td>78 ± 9</td>
<td>81 ± 12</td>
<td>73 ± 9</td>
<td>76 ± 10</td>
</tr>
<tr>
<td>40-49</td>
<td>80 ± 11</td>
<td>96 ± 10</td>
<td>83 ± 8</td>
<td>96 ± 10</td>
<td>73 ± 8</td>
<td>72 ± 7</td>
<td>76 ± 8</td>
<td>80 ± 10</td>
<td>72 ± 7</td>
<td>75 ± 8</td>
</tr>
<tr>
<td>50-79</td>
<td>90 ± 9</td>
<td>110 ± 11</td>
<td>84 ± 8</td>
<td>96 ± 10</td>
<td>83 ± 8</td>
<td>96 ± 10</td>
<td>73 ± 8</td>
<td>72 ± 7</td>
<td>76 ± 8</td>
<td>80 ± 10</td>
</tr>
</tbody>
</table>

**Office measurements**

**SBP (mmHg)**
- Mean ± SD
  - Men: 121 ± 12, 122 ± 11, 125 ± 16, 133 ± 15, 124 ± 14, 110 ± 11, 113 ± 10, 121 ± 17, 130 ± 24, 115 ± 15, 119 ± 15
  - Women: 73 ± 9, 77 ± 8, 86 ± 10, 81 ± 11, 78 ± 10, 71 ± 8, 73 ± 8, 78 ± 9, 81 ± 12, 73 ± 9, 76 ± 10

**DBP (mmHg)**
- Mean ± SD
  - Men: 80 ± 6, 83 ± 9, 84 ± 9, 81 ± 8, 74 ± 6, 75 ± 7, 75 ± 9, 78 ± 9, 75 ± 7, 78 ± 8
  - Women: 80 ± 6, 83 ± 9, 84 ± 9, 81 ± 8, 74 ± 6, 75 ± 7, 75 ± 9, 78 ± 9, 75 ± 7, 78 ± 8

**Ambulatory measurements**

**Daytime**

**SBP (mmHg)**
- Mean ± SD
  - Men: 129 ± 8, 128 ± 9, 129 ± 12, 132 ± 12, 129 ± 10, 118 ± 8, 117 ± 8, 121 ± 12, 136 ± 18, 118 ± 10, 124 ± 12
  - Women: 77 ± 7, 80 ± 6, 83 ± 9, 84 ± 9, 81 ± 8, 74 ± 6, 75 ± 7, 75 ± 9, 78 ± 9, 75 ± 7, 78 ± 8

**DBP (mmHg)**
- Mean ± SD
  - Men: 77 ± 7, 80 ± 6, 83 ± 9, 84 ± 9, 81 ± 8, 74 ± 6, 75 ± 7, 75 ± 9, 78 ± 9, 75 ± 7, 78 ± 8
  - Women: 77 ± 7, 80 ± 6, 83 ± 9, 84 ± 9, 81 ± 8, 74 ± 6, 75 ± 7, 75 ± 9, 78 ± 9, 75 ± 7, 78 ± 8
### Night-time

<table>
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<tr>
<th></th>
<th>SBP (mmHg)</th>
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<tr>
<td></td>
<td>Mean ± SD</td>
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<td>106 ± 11</td>
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### 24 hours

<table>
<thead>
<tr>
<th></th>
<th>SBP (mmHg)</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
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<td>118 ± 11</td>
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Numbers are indicated in parentheses. SBP = systolic blood pressure; DBP = diastolic blood pressure.
blood pressure measurements. The difference between casual and average total blood pressure increases progressively with increasing levels of casual blood pressure. Unfortunately, no ABPM data from an unselected general population including untreated hypertensives are available. However, there is now sufficient data from reasonably large numbers of selected healthy individuals to give a normal range of ABPM (Fig. 6 and Table 5) (115, 116). The importance of night-time blood pressure has been recognized (117−119).

Reference values from these studies allow a range of normality for 24 hours, daytime and night-time blood pressure. It has been agreed on a preliminary basis to classify a total 24-hour blood pressure of \( \geq 135/85 \) mmHg as hypertensive.

Clinical indications (Table 6)

The clinical value of ABPM has not yet been clearly delineated. However, the data available so far support the idea that ABPM provides useful additional information. The placebo effect is avoided with the technique (120, 121) and 'white coat hypertension' is detected (44, 122−125).

Primary hypertension If there is no target-organ damage and blood pressure is in the mild to moderate hypertensive range, mean ambulatory blood pressure similar to the office blood pressure may strengthen the decision to treat. ABPM may have less value if target-organ damage is present and/or office blood pressure is markedly or persistently elevated (e.g. DBP \( \geq 110 \) mmHg) (126, 127).

Secondary hypertension In some forms of secondary hypertension the diurnal profile of blood pressure may be altered and therefore ABPM over 24 hours may offer additional diagnostic information. Examples are pre-eclampsia and hypertension associated with Cushing's disease (128−132). ABPM can also be useful in the diagnosis of pheochromocytoma, particularly when short hypertensive crises do not show plasma catecholamines to clearly increase.

Hypotension There is insufficient information on the applicability of ABPM in patients with intermittent hypotension (e.g. autonomic dysfunction) (132). However, simultaneous 24-hour ECG monitoring and continuous ABPM may be helpful in assessing syncope.

Different working conditions Preliminary results suggest that ABPM may help to establish the diagnosis of hypertension in subjects exposed to job stress and/or unusual daily life rhythm, e.g. shift-workers (15, 133−135) and pilots (136). This may in part demonstrate the superiority of environmental triggers over endogenous circadian rhythm (134−139).

Patients at risk and during rehabilitation It has been suggested that ABPM may be a helpful tool in monitoring patients during rehabilitation after immunosuppressive therapy, especially after renal and cardiac transplantation (140−143) and in post-operative co-arctation patients (144).
TABLE 6. Clinical indications for ambulatory blood pressure monitoring (and simultaneous 24-hour ECG*)

<table>
<thead>
<tr>
<th>Borderline hypertension</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent elevation of clinic pressure with no evidence of target organ involvement</td>
<td></td>
</tr>
<tr>
<td>Discrepancy between home and clinic pressures</td>
<td></td>
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<tr>
<td>Episodic hypertension (e.g. pheochromocytoma)</td>
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<tr>
<td>Demonstration of 24-hour control of pressure</td>
<td></td>
</tr>
<tr>
<td>Evaluation of efficacy and duration of action of antihypertensive agents</td>
<td></td>
</tr>
<tr>
<td>Unexplained adverse events (e.g. hemodynamic symptoms) in hypertensive patients</td>
<td></td>
</tr>
<tr>
<td>Atypical or nocturnal angina pectoris*</td>
<td></td>
</tr>
<tr>
<td>Hypotension (syncope)*</td>
<td></td>
</tr>
</tbody>
</table>

**Evaluation of antihypertensive treatment** ABPM is helpful in identifying patients with apparent treatment resistance by conventional measurement, who have low ABPM values, so that overtreatment is avoided (145 – 148). ABPM is an important technique in the evaluation of antihypertensive efficacy of any drug or treatment regimen in the context of clinical trials (82, 99). The technique enables the assessment of the antihypertensive effect under daily-life conditions and the antihypertensive effect over the entire 24-hour period may be assessed. Ambulatory measurement is a particularly important technique for clinical trials on the antihypertensive effect of single drugs or combined drug regimens (46 – 48, 149 – 152). A placebo effect is not present (120, 121). It can show whether blood pressure is reduced during normal daily activity and whether the effect persists over the entire period between doses. Further, 24-hour mean blood pressure values are more reproducible than conventional blood pressure values so that the number of patients required for antihypertensive drug trials may be considerably reduced (82, 148).

Multiple measurements of blood pressure over a 24-hour period also offer advantages in antihypertensive drug evaluation (Fig. 5) (46, 47, 114, 150 – 154). Ambulatory monitoring of the blood pressure aids in the identification of antihypertensive properties of a given drug in a smaller number of subjects than when using casual single blood pressure determinations. It appears that this is due both to a reduction in variance on repeated determinations of mean blood pressure over time and to eliminating the confounding pressure response of the patient to the medical care environment (122, 123, 155, 156).

**Prognostic importance**

The ultimate test of the clinical usefulness of non-invasive ABPM is the degree to which it can assess the risk of cardiovascular morbidity in comparison with conventional blood pressure measurements (47, 155, 156). There are theoretical reasons for supposing that larger numbers of readings taken in more natural circumstances may improve this assessment. Furthermore, there is agreement from a large number of studies that 24-hour daytime mean blood pressure values can be more closely correlated than conventional blood pressure values with the target-organ damage associated with hypertension (157, 158). This has been observed for echocardiographically assessed left ventricular hypertrophy (155, 159, 160), which has the
dual advantages of being the most sensitive measure of target-organ damage and of being an important and independent predictor of cardiovascular morbidity and mortality (155, 159, 161, 162). It has also been observed for other indices of hypertension-related complications such as microalbuminuria (163), pulse wave velocity (an index of arterial stiffness) and a score derived from a history of cardiovascular complications, ECG, chest X-ray and fundoscopic changes originally proposed by Sokolow and his colleagues (164). It is not clear whether any particular value or time segment of the 24-hours is paramount in predicting the consequences of hypertension. In some studies, left ventricular hypertrophy was greater in those hypertensives with lesser blood pressure falls at night or those who had higher blood pressures at work (155, 165). Further, the standard deviation of 24-hour blood pressure has been correlated with target-organ damage, suggesting that not only mean ambulatory blood pressure but also blood pressure variability may be important (125).

While these studies suggest that ABPM has prognostic value, it is difficult to draw causal inferences from cross-sectional studies and so far there is only limited evidence on the relationship between ambulatory blood pressure values and the incidence of cardiovascular morbidity and mortality. One study (156) contained only preliminary results from a larger database which is still being compiled. In another study (158) ambulatory blood pressure was shown to be superior to office blood pressure in predicting cardiovascular morbidity and mortality. However, the ambulatory blood pressure was recorded only at entry to the study and the effect of treatment on blood pressure and prognosis was not reported. Further, only daytime values were recorded.

The evidence that ABPM can improve the assessment of prognosis for hypertension is thus encouraging but incomplete. A prospective controlled study is required to address the question of whether ambulatory blood pressure is a significantly better predictor of cardiovascular morbid and fatal events than office blood pressure and/or adds to the prediction offered by office blood pressure. While it may be impractical to take cardiovascular events as the outcome variable, useful information may be obtained by assessing the development of intermediate markers of cardiovascular disease such as left ventricular hypertrophy. Such a study may be further complicated by the potentially confounding effect of antihypertensive treatment. For the time being, therefore, office blood pressure should be taken as the primary indicator of prognosis.

Costs

The cost of the hardware (monitor, interface, solid-state memory system) is considerable (＞US $10,000) and the need for computer equipment makes it even greater (166–168). However, a large percentage of people initially labeled as having mild hypertension may later be shown with ABPM to have average pressures below the lower limit of the hypertensive range (169). In patients with mild hypertension, ABPM has shown that up to 40% of subjects have pressures low enough to withhold antihypertensive treatment; a projection for the effect of this decision on the relative cost over short periods has been made. However, this simplified approach omits many factors requiring investigation, including the establishment of normal values
and of blood pressure levels that require treatment, and whether cardiovascular morbidity and mortality can actually be reduced. Until information on these issues is available, no calculation of overall costs or any real assessment of genuine benefits from the long-term use of ABPM can be made. Initial observations have suggested that ABPM need not invariably increase the cost of care in mild hypertension. Further, this new technique may direct antihypertensive therapy to those with higher average pressures; aggressive treatment of this group might be more effective in achieving a reduction in long-term cardiovascular morbidity, by tailoring therapy to the individual patient and reducing side effects.

Research perspectives

Research directions in the comparatively new field of ABPM require a description of the population distribution of ABPM parameters including day, night, 24 hour, day–night difference, variability and clinic ABPM difference. Population studies are required to determine normal ABPM values for certain populations, e.g. children (63), the elderly (171–173), pregnant women (129, 174), and different cultural and racial groups (175).

Prospective epidemiological studies relating ABPM parameters to morbidity and mortality are progressing and need to be performed in larger trials. This will support the hypothesis that treatment is clearly indicated above certain levels of ABPM.

In addition, the independent prognostic significance of blood pressure variability, the alerting response, night-time blood pressure and day–night difference above that of mean day-time blood pressure is not well-known and should be studied in longitudinal studies.

IV. CONCLUSIONS

The availability of fully automated portable reliable monitors for non-invasive ambulatory blood pressure monitoring has improved our understanding of blood pressure variability. With the new generation of ABPM recorders using oscillometric and/or auscultatory techniques, it is possible to obtain at least 24-hour ambulatory measurements.

Technically, the portable monitors still need some improvements. Weight and pump noise have been considerably improved, but the smaller and quieter the recorders the better. The reliability of the energy sources and recording efficiency is acceptable. It is not possible, however, to apply these measuring systems during unrestricted conditions. In more than 20% of subjects, sleep disturbances occur due to discomfort of the cuff pressure or pump noise and complicate assessment of the nocturnal profile. A complete 24-hour blood pressure profile is necessary to include early morning hours and the awakening phase. These recordings are of particular interest in assessing cardiovascular risk. This is substantiated by more recent investigations that demonstrate a morning (8.00 – 10.00 a.m.) peak in the incidence of myocardial infarction (13, 22 – 24, 176). The significance of these observations for cardiovascular or cerebrovascular diseases and the increased incidence of angina pectoris or cerebral ischemia during the relatively hypotensive nocturnal phases.
make it necessary to carry out reliable long-term blood pressure measurements during the night as well. There is some evidence that hypertensive patients who do not have a nocturnal fall in blood pressure (non-dippers) are at greater risk that the majority who show a significant reduction in nocturnal blood pressure (dippers) (177). The possibility also exists that antihypertensive drugs with a prolonged duration of effect, or administered frequently, may cause a profound reduction in nocturnal blood pressure in ‘dippers’, and that such hypotension may lead to myocardial ischemia and infarction.

The benefits of ambulatory blood pressure monitoring in the assessment of the efficacy of drug treatment are now well established. Conventional clinic measurement and home blood pressure (178 – 183) are influenced by many factors which make the technique unsuitable for research into drug efficacy, but, more importantly, clinic measurement cannot provide assessment of duration of effect, or of the effect of antihypertensive drugs on sleeping pressure. If it can be confirmed that non-invasive ambulatory blood pressure measurement is free of any placebo effect (121, 184), then it is possible that the design of antihypertensive drug studies could be greatly simplified. The greatest potential for ambulatory blood pressure measurement in assessing drug efficacy may be its ability to reduce significantly the numbers of patients needed in such studies. The time has surely come when studies of antihypertensive drug efficacy which do not assess blood pressure over 24 hours should no longer be acceptable.

Although physician and ambulatory blood pressure recordings are highly correlated, disparities are common, with daytime or workplace ambulatory pressure being lower in most but higher in some patients (182, 183). As many as 20% of adults currently diagnosed as hypertensive are normotensive outside the doctor’s office, thus exhibiting white-coat hypertension (122, 123). As expected from previous results, patients with office hypertension but normal ambulatory blood pressures appear to have normal left ventricular structure and function (155). Since both echocardiographic left ventricular hypertrophy (185 – 191) and elevated ambulatory blood pressure predict an adverse prognosis, it appears that many patients currently classified as hypertensive may instead have a benign hyperreactivity of blood pressure to physician measurement. Further research is needed to verify this and to determine whether patient outcome is improved by the use of ambulatory pressure measurements or echocardiographic left ventricular mass measurements as a basis for instituting or modifying antihypertensive treatment.

Hypertensives with confirmed left ventricular hypertrophy show an increased incidence of complex ventricular arrhythmias (192) and sudden cardiac death: this makes it desirable that ambulatory measurement should also permit simultaneous long-term electrocardiography and this should be available for clinical research in the near future.

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12. Characterization of blood pressure variations with ambulatory monitoring

Thomas G. Pickering

The measurement of blood pressure is one of the most important in clinical medicine, but also one of the most unreliable. In part this unreliability is due to the inherent limitations of the currently available non-invasive techniques, but these may be overshadowed by the fact that blood pressure is not a fixed entity, and is subject to enormous variability from moment to moment. In the clinical evaluation of hypertensive patients it is customary to make at most 2 or 3 measurements of blood pressure at one visit, which are assumed to be representative of that patient's average or 'true' blood pressure in the interval between successive clinic visits. It is now possible to test the validity of this assumption using ambulatory monitoring techniques, which also provide the opportunity to explore the causes and consequences of such variations.

I. SPONTANEOUS SHORT-TERM VARIABILITY

As shown schematically in Figure 1, a number of discrete sources of blood pressure variability can be identified. At the high-frequency end of the spectrum are respiratory fluctuations, followed by Mayer waves. Ultradian variations, with a periodicity of 90 minutes, are not clearly established in man. These spontaneous variations can be masked by the effects of superimposed physical and mental activity, so they are best studied in a steady-state condition.

Short-term blood pressure variability, of which respiratory fluctuation is the dominant cause, can only be assessed by beat-to-beat monitoring, e.g. using intra-arterial recording. Mancia and colleagues (1) studied blood pressure and heart rate variability in a series of normotensive and hypertensive individuals using intra-arterial ambulatory monitoring. Variability was expressed as the standard deviation (i.e. the absolute level) and variation coefficient (i.e. the percentage level), measured over two intervals: 30 minutes (short-term variability) and 24 hours (long-term variability) calculated from the hourly averages. The short-term variability was
about two-thirds of the magnitude of the long-term variability. One of their principal findings was that both the mean levels and the short-term variabilities of blood pressure and heart rate tend to change in parallel; thus during sleep there is a decrease not only of blood pressure and heart rate, but also of their variabilities. These within-subject changes of variability are shown in Figure 2.

With increasing age, there is an increase of short-term blood pressure variability, but a decrease of heart rate variability (1).

II. RESPIRATION AND BLOOD PRESSURE VARIABILITY

The respiratory variations in blood pressure were studied by Dornhorst and colleagues (2), who established a number of important associations. At normal rates of breathing the pressure falls during most of inspiration, but at slower rates inspiration is associated with a rising pressure. Sinus arrhythmia, i.e. the change of heart rate associated with respiration, does not contribute to the blood pressure change; this statement was based on the observation that the appearance and disappearance of sinus arrhythmia did not alter the rhythm of blood pressure. During periods of apnea rhythmical variations of blood pressure may still be apparent, at a rate of 6 per minute (0.1 Hz), which are usually known as Mayer waves. Finally, the fluctuations of blood pressure are more marked when standing than when supine.
**Fig. 2.** Comparison of between- and within-subject changes of short-term blood pressure variability as a function of the average pressure. Data plotted from Mancia et al. (1).

### III. POWER SPECTRAL ANALYSIS OF BLOOD PRESSURE AND HEART RATE VARIABILITY

It has been known for many years that both heart rate and blood pressure exhibit rhythmical fluctuations, of which respiratory sinus arrhythmia and Mayer waves are examples. Using the techniques of power spectral analysis it has recently become possible to quantify these fluctuations, and to relate them to the two limbs of the autonomic nervous system, the sympathetic and the vagues.

The technique was first developed for heart rate variability, and was based on analysis of the beat-to-beat variations occurring during steady-state conditions, with the respiration rate held constant. In man there are two peaks, at 0.1 and 0.25 Hz (3).

The contributions of the sympathetic and parasympathetic systems to these peaks have been demonstrated with selective autonomic blockade, e.g. using atropine and propranolol (3, 4). Moving from the supine to the upright position causes a relative increase in the low-frequency/sympathetic activity peak, and a relative decrease in the high-frequency/vagal activity peak (3, 5).

Pagani and colleagues (6) have analyzed heart rate and systolic pressure variabilities in 24-hour recordings made with a catheter-tipped (and hence high-fidelity) transducer in ambulatory hypertensive patients. During the day there was a predominantly low-frequency (approximately 0.1 Hz) component, which was more evident in the pressure than in the heart rate spectrum. The high-frequency component (0.25 Hz) was detectable only at night, when it was present in both traces. In a study of hospitalized patients Furlan and colleagues (7) were able to demonstrate a diurnal rhythm of sympathetic activity (measured as the low-frequency blood pressure oscillations) which was maximal at about 9:00 a.m., and lowest during the night.
IV. FACTORS INFLUENCING INDIVIDUAL DIFFERENCES IN BLOOD PRESSURE VARIABILITY

The factors which influence blood pressure variability, other than the level of the blood pressure and the role of the baroreceptors (see below), have received relatively little attention. There is general agreement that variability assessed by ambulatory monitoring increases with age (8, 9), which may be partly accounted for by the diminished baroreflex sensitivity associated with aging, although other factors may also be involved (9). Ambulatory blood pressure variability has also been reported to be increased in high-renin patients (9).

The baroreceptors

It has long been recognized that the aortic and carotid sinus baroreceptors play a buffering role in the regulation of blood pressure. A consistent finding from intra-arterial ambulatory monitoring studies has been that subjects with diminished baroreflex sensitivity show increased blood pressure variability, with a negative correlation between the two (10—12). Indeed, when comparing the associations between age, mean arterial pressure, and baroreflex sensitivity with blood pressure variability, Floras and colleagues (12) found that only baroreflex sensitivity was a significant predictor. Conway and colleagues (13) found that subjects with high baroreflex sensitivity showed greater heart rate variability during ambulatory monitoring and a smaller fall of blood pressure during the night than subjects with lower reflex sensitivity.

The baroreceptors may modulate the blood pressure changes occurring in response to physical or mental activity: Conway and colleagues (13) found that the increase of pressure during mental arithmetic was greatest in subjects with the lowest baroreflex sensitivity, and Floras and colleagues showed the same thing during dynamic exercise (14).

The central nervous system

A characteristic finding of baroreceptor modulation of blood pressure variability is that when blood pressure is increasing, for much of the time heart rate and blood pressure rise and fall together. In such situations, the central nervous system can be assumed to be playing the primary role in regulating blood pressure.

In man, blood pressure varies over 24 hours in parallel with changes in plasma catecholamines (15), although individual differences in resting plasma catecholamine levels are not correlated with differences in blood pressure variability (8).

V. PHYSICAL AND MENTAL ACTIVITY

If the effects of environmental stimuli and changes in physical activity are minimized, the profile of blood pressure during the day becomes relatively flat, with a fall of about 20% occurring during sleep (16, 17). It has also been shown that diurnal blood pressure changes are less pronounced in hospitalized patients than in patients
studied in their natural environment (18). Both the average level of blood pressure and its variability are reduced during periods of bed rest as compared to periods of physical activity (19).

A number of commonly occurring daily activities have been shown to influence the changes of blood pressure recorded during ambulatory monitoring. We found that 15 such activities could account for nearly half of the overall blood pressure variance (20). The average effects on blood pressure are listed in Table 1.

**Posture** This is an important source of blood pressure variance, particularly in ambulatory monitoring studies. Changing from the supine to the upright position causes an increase of diastolic pressure with little or no change of systolic. In ambulatory monitoring studies Gellman et al have claimed that changes of posture account for a major portion of overall blood variance (33% of systolic, and 47% of diastolic) (21). However, their analysis included walking as a postural component, as well as standing, and much of this effect can be explained by the effects of the activities associated with different postures rather than the postures themselves, because the changes of blood pressure occurring simply as the result of changing posture are rather modest.

**Dynamic exercise** This raises systolic pressure and heart rate, with little effect on diastolic pressure. In normotensive subjects systolic pressure during intense exercise may reach 200 mmHg or more.

**Static (isometric) exercise** This activity, such as occurs during weight-lifting, produces a very different blood pressure response, with a marked increase of both systolic and diastolic pressure. The extent of this increase is a function of the inten-

**TABLE 1. Average changes of blood pressure associated with 15 commonly occurring activities**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meetings</td>
<td>+20.2</td>
<td>+15.0</td>
</tr>
<tr>
<td>Work</td>
<td>+16.0</td>
<td>+13.0</td>
</tr>
<tr>
<td>Transportation</td>
<td>+14.0</td>
<td>+9.2</td>
</tr>
<tr>
<td>Walking</td>
<td>+12.0</td>
<td>+5.5</td>
</tr>
<tr>
<td>Dressing</td>
<td>+11.5</td>
<td>+9.7</td>
</tr>
<tr>
<td>Chores</td>
<td>+10.7</td>
<td>+6.7</td>
</tr>
<tr>
<td>Telephone</td>
<td>+9.5</td>
<td>+7.2</td>
</tr>
<tr>
<td>Eating</td>
<td>+8.8</td>
<td>+9.6</td>
</tr>
<tr>
<td>Talking</td>
<td>+6.7</td>
<td>+6.7</td>
</tr>
<tr>
<td>Desk work</td>
<td>+5.9</td>
<td>+5.3</td>
</tr>
<tr>
<td>Reading</td>
<td>+1.9</td>
<td>+2.2</td>
</tr>
<tr>
<td>Business (at home)</td>
<td>+1.6</td>
<td>+3.2</td>
</tr>
<tr>
<td>Television</td>
<td>+0.3</td>
<td>+1.1</td>
</tr>
<tr>
<td>Relaxing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sleeping</td>
<td>−10.0</td>
<td>−7.6</td>
</tr>
</tbody>
</table>

Changes are shown relative to blood pressure while relaxing.
ty of contraction rather than of the bulk of muscle being used: at 50% of maximal voluntary contraction mean arterial pressure may increase by 40 mmHg within 1 minute (22).

Sexual intercourse Sexual intercourse, another form of exercise, can produce a dramatic transient rise of pressure, ranging from 25 to 120 mmHg in systolic, and 24 to 48 mmHg in diastolic (23). These changes are reversed within a few minutes after orgasm.

Ingestion of food and drink In younger subjects there is a decrease of diastolic pressure, and little change of systolic pressure 3 hours after a meal (24, 25). In older subjects there may be a pronounced fall of both systolic and diastolic pressure after food (26).

Smoking Smoking a cigarette raises both heart rate and blood pressure. In patients who were studied smoking in their natural environment during intra-arterial ambulatory blood pressure monitoring Cellina and colleagues (27) found increases of about 11/5 mmHg, sometimes preceded by a transient fall of pressure; changes were quantitatively similar in normotensives and hypertensives. The effect on blood pressure is seen within a few minutes, and lasts about 15 minutes.

Alcohol Alcohol may increase heart rate, with small but variable effects on blood pressure in normal subjects, ranging from no significant change to an increase of 5/7 mmHg at 1 hour after ingestion of alcohol (28, 29).

Caffeine Caffeine increases blood pressure, plasma catecholamines, and renin, but not heart rate (30). The increase of blood pressure begins within 15 minutes of drinking coffee, and is maximal in about 1 hour, and may last for as much as 3 hours. Coffee and cigarettes are often taken together, and a study by Freestone and Ramsay showed that they may have an interactive effect (31). As shown in Figure 3,
smoking a cigarette elevated blood pressure for 15 minutes, whereas drinking coffee had no effect for an hour, when there was a significant increase. When the cigarette and coffee were taken together, however, there was a significant increase of pressure of about 10 mmHg, which was seen within 5 minutes, and was still present 2 hours later.

**Talking** Talking is potent pressor stimulus that has both physical and psychological components, which have been extensively investigated by Lynch and colleagues (32–36). Reading aloud produces an immediate increase of both systolic and diastolic pressure (by about 10/7 mmHg in normotensive individuals) and of heart rate, with an immediate return to baseline levels once silence is resumed (32). Speaking fast produces a bigger increase than speaking slowly (34). The role of psychological factors is shown by the finding that talking in front of a group produces a bigger increase than reading aloud while alone (32). Of particular relevance to the clinic measurement of blood pressure is the perceived status of the person being spoken to: an experimenter posing as a physician will evoke higher pressures than one posing as an experimenter with equal status to the subject (33). The size of the audience is also a factor (35).

**Mental activity and emotion** At least two studies have reported some correlation between self-rated mental 'stress' or 'arousal' and blood pressure during non-invasive ambulatory monitoring (37, 38). We have reported higher levels of blood pressure when people are at work than when they are at home, which we have attributed to mental rather than to physical factors, because most of our subjects had sedentary jobs (39, 40).

Mood has also been reported to be a potent determinant of blood pressure during ambulatory monitoring. We have found that self-reported levels of anger, anxiety and happiness are correlated with blood pressure: systolic pressure decreased as the intensity of happiness increased, and diastolic pressure increased with the intensity of anxiety (41).

**VI. COMPARISON OF BLOOD PRESSURE VARIABILITY IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS**

Several studies using intra-arterial ambulatory monitoring have shown that blood pressure variability, usually measured as the standard deviation of the daytime pressure, tends to be higher in hypertensives than in normotensives (8, 42, 43). However, if variability is normalized by calculating the variation coefficient, the difference between normotensives and hypertensives becomes much smaller (8). Floras and colleagues found that increased blood pressure variability was related not only to higher mean pressures, but also to increased age and diminished baroreflex sensitivity (43). Multiple regression analysis showed that the only independent predictor of variability was baroreflex sensitivity.

We compared 4 measures of blood pressure variability or reactivity in 3 groups of subjects (58 normotensives, 578 mild hypertensives with clinic blood pressures below 160/106 mmHg, and 66 established hypertensives with clinic pressures above
160/105 mmHg), all of whom wore a non-invasive blood pressure monitor for 24 hours (44). The first measure was the change of pressure from work to home, which was greater in the hypertensives than in the normotensives (for systolic pressure, the changes were 3, 8 and 7 mmHg respectively for the 3 groups), and the change between home and sleep, which was no different (12, 14 and 13 mmHg respectively). The second was blood pressure variance, which showed a progressive increase with the level of pressure (the average daytime values being 130, 145 and 244 mmHg for systolic pressure for the 3 groups), as shown in Figure 4. The third measure was the range (defined as the difference between the upper and lower 5% of readings). This also was bigger in the hypertensive groups. Finally, the blood pressure response to specific activities (both physical and mental) was greater in the hypertensive group.

Other studies comparing blood pressure changes occurring during physical or mental activity have given a less clear-cut picture. The increase of systolic pressure during dynamic exercise is normal in patients with borderline hypertension, but exaggerated in those with more severe disease (45, 46). The maximal exercise capacity may be reduced in hypertension, however (47). Elderly hypertensives show similar blood pressure responses to age-matched normotensive subjects (48).

VII. CAN BLOOD PRESSURE VARIABILITY CHANGE INDEPENDENTLY OF THE AVERAGE LEVEL?

It has been clear for many years that blood pressure variability is closely related to the average level of pressure, being greatest when the pressure is high, as during vigorous exercise, and at its minimum during sleep. This relationship has been quan-
tified by Mancia's group (see Fig. 2) and shown to apply for both absolute and relative measures of variability.

That this relationship is not invariable has been demonstrated in a study by van der Meiracker and colleagues (49). Patients with mild untreated hypertension were studied in hospital with intra-arterial 24-hour monitoring. Half the subjects were ambulatory during the day while the others remained in bed for the entire 24 hours. The ambulatory subjects had higher average levels of pressure during the day than the subjects in bed, but their variability (measured as the standard deviation) was not significantly higher, as shown in Figure 5. Furthermore, 'sensory deprivation' (resting quietly with the eyes open) did not affect the mean blood pressure in comparison to simple bed rest, but did result in a marked reduction of blood pressure.

*Fig. 5.* Hourly changes of blood pressure and heart rate in subjects who were either ambulatory during the day (open circles) or recumbent for 24 hours (closed circle). The hatched area represents a period of sensory deprivation. Reproduced by courtesy of Van der Meiracker et al. (49).
Fig. 6. Typical blood pressure changes during sleep in a normal subject. Upper trace shows sleep stages (W = waking, St. 1, 2, 3, 4 = Stages 1, 2, 3, 4). Blood pressure is plotted every 60 seconds, and every 30 seconds during REM sleep to show increase variability. Reproduced with permission from Coccagna et al. (51).

variability (Fig. 5). These results suggest that the effects of physical and mental activity on the blood pressure level and its variability can be dissociated from each other.

VIII. CHANGES OF BLOOD PRESSURE ASSOCIATED WITH SLEEP AND WAKEFULNESS

During the first hour of sleep there is normally a progressive fall of blood pressure, which usually shows it maximal decrease of 15–20% 2 hours after sleep onset (50–57), as shown in Figure 6. This coincides with the deepest stages of slow-wave sleep (Stages 3 and 4). During REM sleep the blood pressure is at about the same level as in Stage 2 (approximately 10% less than during wakefulness) but is much more variable, with fluctuations of as much as 30 mmHg over a few minutes (50).

Blood pressure rises immediately on waking. The close association between blood pressure and the level of arousal is further shown by the fact that in a drowsy subject the appearance of episodes of alpha rhythm (which signifies arousal) is accompanied by surges of arterial pressure (53). The contrasting effects of sleep and wakefulness on blood pressure were well demonstrated in a study by Athanassiadis and colleagues (56): in patients on an accident ward, whose physical activity was limited by plaster casts, blood pressure remained relatively constant during the day, and fell consistently by about 25% during sleep.

IX. IS THERE A CIRCADIAN RHYTHM OF BLOOD PRESSURE?

Recordings made over 24 hours in ambulatory subjects, using either invasive (58) or non-invasive recorders (20), have typically shown that blood pressure tends to be highest in the morning, with a gradual decrease over the course of the day, and
Fig. 7. Diurnal rhythms of blood pressure on 3 different work shifts: (a) daytime shift, (b) first day of night shift, (c) last day of night shift. Reproduced with permission from Sundberg et al. (63).
lowest during the night (Fig. 7). This observation led to the suggestion that there might be an intrinsic circadian rhythm of blood pressure analogous to the circadian pattern of cortisol or body temperature. The case for an intrinsic sinusoidal pattern of blood pressure variation has been argued most forcefully by Halberg, who found that such curves fitted the blood pressure pattern of subject kept in confined environment for a period of several days (58). It has also been proposed by Raftery that there is a gradual increase of blood pressure during the early morning hours (3 a.m. to 6 a.m.) before the time of wakening, and that this increase could contribute to the high incidence of cerebral hemorrhage and myocardial infarction in the early morning (57). Other workers, however, have presented data which indicate that the apparently sinusoidal pattern of blood pressure is largely an artifact attributable to the averaging of records from individuals who wake at different times: when the recordings are synchronized to the time of waking rather than the time of day, the early morning rise of pressure is no longer seen (60, 61). Instead, blood pressure remains relatively stable during the hour before waking, but rises abruptly at the moment of waking. This pattern is consistent with studies where EEG was recorded as well as blood pressure (57).

Mancia and colleagues examined the average blood pressure levels over consecutive 30-minute periods throughout the 24 hours and also found no early morning increase preceding waking (62). All the half-hour averages during waking were substantially similar, leading them to conclude that there is no circadian rhythm of blood pressure. The relatively flat profile of blood pressure during the day observed in their study may be attributed to the fact that their patients were hospitalized.

The question whether there is an endogenous circadian rhythm of blood pressure, or whether the changes can be accounted for by variations in activity, is an important one. It can best be answered by removing the influence of external stimuli, so that if the rhythm persists, it can be attributed to endogenous factors. This was done in the study by Athanassiadis and colleagues (56), in which blood pressure was monitored non-invasively for 24 hours in patients in an orthopedic ward, who were immobilized by plaster casts. In this situation the blood pressure showed no evidence of any sinusoidal change, being relatively constant during the day, and decreasing during sleep. There were in effect two levels of pressure, one corresponding to waking, and the other to sleeping.

**Shift workers** Studies of shift workers have also shown a close linkage between activity and blood pressure (63–66). Sundberg and colleagues monitored 24-hour pressure and heart rate in 7 normotensive nurses on 3 different days (63). On the first day they worked a normal daytime shift, and showed a typical diurnal pattern, with the highest pressures during work and the lowest pressures at night (see Fig. 7). The second recording was made on the first day they worked a night shift, and showed a complete reversal of the diurnal blood pressure pattern, with the lowest blood pressure occurring while they were asleep during the day. The third recording, made a few days later, was similar to the second. In contrast to the immediate reversal of the blood pressure rhythm, the diurnal rhythm of heart rate was still not fully reversed by the third recording.
X. CHRONOBIOLOGICAL ANALYSIS OF DIURNAL BLOOD PRESSURE VARIATIONS

A large number of biological variables show an intrinsic rhythmicity with a period of approximately 24 hours, hence the term circadian ('around the day') rhythms. Halberg and colleagues (59) have been a strong advocate of the use of 'rhythmometry' to analyze human diurnal blood pressure patterns. The basis of this approach is to analyze the observed patterns as a series of cosine waves, with a basic period of 24 hours. A number of terms need to be defined for this analysis. The mesor* is the mean level, which is close (but not necessarily identical) to the average 24-hour blood pressure; the amplitude is the distance from the peak (or trough) to the mesor, which in this case would be the difference between the average 24-hour pressure and the peak pressure. On this schema, hypertension can be classified as 'mesor hypertension' when the entire profile is shifted to a higher level, or 'amplitude hypertension'. Ideally, this type of analysis should be performed over periods of more than 24 hours, preferably 48 hours.

While this approach has a mathematical appeal, it may be criticized on two grounds. First, the available evidence overwhelmingly suggests that blood pressure is not determined by an endogenous rhythm to the same extent that, for example, heart rate or plasma cortisol are, and second, it imposes a symmetry that may be more artificial than real. Thus, the peak and trough of blood pressure are assumed to be exactly 12 hours apart, and also equidistant from the mesor. Neither of these criteria is likely to be met in reality. The fit between the theoretical waveform and the observed data points can be improved by including as many as four harmonics in the Fourier analysis (66), but the physiological relevance of this is questionable.

XI. COMPARISONS OF DIURNAL PATTERNS IN NORMAL AND HYPERTENSIVE SUBJECTS

In patients with hypertension the diurnal pattern of blood pressure change is generally similar to the changes occurring in normotensive subjects, except that the entire blood pressure profile is shifted upward (Fig. 8). Thus, the differences between work and home pressures, and between home and sleep pressures are approximately the same in normotensive and hypertensive subjects (about a 20% decrease during sleep in both cases) when expressed on a percentage basis, although in absolute terms they may be greater in hypertensives (54, 67, 68).

XII. SLEEP-DISORDERED BREATHING AND THE SLEEP APNEA SYNDROME

A wide spectrum of severity of sleep-disordered breathing has been recognized, with snoring at the benign extreme, and obstructive sleep apnea at the other. These condi-

*The word mesor is derived from the Midline Estimating Statistic Of Rhythm.
Fig. 8. Comparison of clinic and diurnal blood pressure changes in 3 groups of subjects for systolic (upper panel) and diastolic pressure (lower panel). Closed circles = normotensives; solid squares = mild hypertensives; open circles = established hypertensives. Reproduced with permission from Harshfield et al. (44).

...tions are relevant to the present discussion, not only because they affect the changes of blood pressure occurring during sleep, but also because they are significant risk factors for cardiovascular disease.

The hemodynamic changes occurring during the apneic episodes have been well described by Tilkian and colleagues (69). As the apnea develops there is systemic oxygen desaturation and an abrupt elevation of arterial pressure, without any accompanying tachycardia. In Tilkian's study there were quite marked increases in the level of blood pressure during sleep, the average change being from 139/85 mmHg during wakefulness to 167/105 mmHg during sleep. However, in elderly subjects, apneic episodes may be associated with hypotension (70).
XIII. OTHER CONDITIONS IN WHICH THE NORMAL DIURNAL PATTERN OF BLOOD PRESSURE IS ALTERED: DIPPERS AND NON-DIPPERS

There are some situations in which the fall of blood pressure during sleep in hypertensive patients may be absent or reversed. Patients showing this phenomenon have been referred to as 'non-dippers', to distinguish them from the normal 'dippers' (71, 72). Such conditions are of interest for several reasons: first, they may be helpful in understanding the regulation of blood pressure during sleep and wakefulness; second, the findings of an absent nocturnal blood pressure fall may be of diagnostic value; and third, it may have prognostic value as well. A problem that is sometimes overlooked is that the observation of an absent nocturnal fall of blood pressure may simply be due to the fact that the patient did not sleep, or if non-invasive blood pressure monitoring was used, was aroused by the inflation of the blood pressure cuff. However, in the conditions in which the diurnal rhythm of blood pressure is abnormal there is usually a decrease of heart rate during the night, which should help distinguish the non-dippers from the non-sleepers. These conditions are described below, and listed in Table 2.

There is some controversy as to whether hypertensive patients with left ventricular hypertrophy (LVH) show the same diurnal variation of blood pressure as those without. According to Raftery (73) the pattern is similar, but a recent study by Verdecchia and colleagues (74) found that patients whose pressure remained high during the night were more likely to have LVH hypertrophy. What is not clear from this study is whether the development of LVH affects the diurnal pattern of blood pressure, or whether a persistent elevation of pressure throughout the day and night accelerates the development of LVH.

**Malignant hypertension.** Shaw and colleagues (75) monitored the blood pressure in hospitalized and recumbent patients using a non-portable non-invasive monitor. They divided them into two groups according to the fundal changes. The first group was classified as having benign hypertension, and their second group, malignant

<table>
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<th>TABLE 2. Conditions in which the normal nocturnal fall of blood pressure is blunted</th>
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hypertension. Blood pressure fell during sleep in the benign group by 15/9 mmHg, but showed no change in the malignant group.

**Chronic renal disease** Patients with chronic renal disease show a marked attenuation of the nocturnal blood pressure fall in comparison to control groups (76). The decrease of heart rate is still present, although somewhat attenuated.

**Pheochromocytoma** Patients in whom pheochromocytoma is suspected are obvious candidates for ambulatory monitoring. Littler and Honour (77) were the first to report that the nocturnal fall of blood pressure may be absent (in 2 out of the 3 patients they studied). However, in a subsequent study of 8 patients Imai and colleagues found that this was the exception rather than the rule (78).

**Pre-eclamptic toxemia** During normal pregnancy there is a normal fall of blood pressure during sleep (79), but in patients with pre-eclamptic toxemia this fall may be absent or reversed, with an increase of pressure during sleep (79–81).

**Cushing’s syndrome** Munakata and colleagues (82) studied 15 patients with Cushing’s syndrome (11 of pituitary origin and 4 adrenal) and found that the normal nocturnal fall of blood pressure was absent, although the usual decrease of heart rate persisted. That this phenomenon was attributable to glucocorticoids was supported by the finding that patients with chronic glomerulonephritis or systemic lupus erythematosus also had no nocturnal fall of blood pressure when treated with prednisone, but a normal fall when untreated (83).

**Orthostatic hypotension** Patients suffering from idiopathic orthostatic hypotension have been found to exhibit a paradoxical elevation of pressure during the first part of the night, and the lowest pressures of the day during the morning, when they are typically most symptomatic (84).

**Diabetes mellitus with autonomic neuropathy** Autonomic neuropathy is a not uncommon complication of insulin-dependent (Type I) diabetes, and has been attributed to interruption of both vagal and sympathetic control of the circulation. The former is manifested by a relatively fixed heart rate, and the latter by orthostatic hypotension. In common with patients with idiopathic orthostatic hypotension, blood pressure remains high during the night (85).

**Congestive heart failure** Caruana and colleagues (86) studied patients with congestive heart failure, all of whom had had a previous myocardial infarction. Neither blood pressure nor heart rate showed much change during the night, particularly in those patients who had the lowest ejection fractions.

**Cardiac transplantation** Cardiac denervation is another situation where pressure increases at night. This has been observed in patients with cardiac transplants (85, 87). The nocturnal bradycardia is still present.
XIV. AMBULATORY MONITORING IN SPECIAL POPULATIONS

Children

Two studies have described diurnal blood pressure patterns in healthy normotensive children during a school day. In the first, by Egger and colleagues (88), 20 girls and 23 boys aged 10−16 years showed similar diurnal patterns, with a nocturnal decrease of blood pressure of 11% in the girls and 9% in the boys. Blood pressures were somewhat higher in the boys, but the boys were studied on a school day, while the girls were studied on a weekend day. Ambulatory blood pressure was positively correlated with the age, body weight, and height of the children, confirming data obtained from casual readings (89).

In the second study, Wilson and colleagues (90) reported data from 178 adolescents aged 13−19 years (of whom 60% were girls) during a school day. Subjects were classified as cases if they had at least one hypertensive parent, and as controls if both parents were normotensive. The main object of the study was to see if ambulatory pressure gave a better discrimination between cases and controls than casual pressure. There was no significant difference in casual systolic pressure between the two groups, and a marginally \( P = 0.053 \) significant difference in diastolic (see their Table 9.6). There were no significant difference in the unadjusted ambulatory pressures between the two groups, but after adjusting for the influence of other variables such as physical activity, the effects of the causal blood pressures were no longer significant, and there was a significantly \( P = 0.005 \) higher diastolic pressure in the cases than in the controls.

Pregnant women

The measurement of blood pressure during pregnancy is of particular importance because hypertension may put both the mother and the fetus at risk. As with hypertension in the non-pregnant state, the relationship between risk and blood pressure is a continual one (91). The situation is complicated by the fact that blood pressure decreases during normal pregnancy, so that repeated and reliable monitoring is desirable. In a normal pregnancy this decrease reaches 10−15 mmHg in systolic and diastolic pressure by 16−20 weeks with a slow return to non-pregnant levels thereafter (92). In women with essential hypertension this fall may be even larger, but if this does not occur the prognosis is poor (93).

The role of ambulatory monitoring has also been relatively neglected, but, as described above, pre-eclamptic toxemia is one of the numerous conditions in which the normal diurnal rhythm of blood pressure may be absent or even reversed. Data for the range of ambulatory pressures in normotensive pregnant women are scanty, but in a small study of 11 women in their third trimester, Margulies and colleagues (94) quote values of 110 ± 7 mmHg while awake, and 71 ± 5 mmHg while asleep, giving a nocturnal decrease of pressure of 12%. The highest pressures occurred between 7:00 and 10:00 p.m. This is in contrast to the normal diurnal patterns seen in normotensive pregnancy and in patients with essential hypertension. Ambulatory monitoring thus has the potential of discriminating between patients with pre-eclampsia and essential hypertension.
Elderly

There appears to be no great difference in the diurnal rhythm of blood pressure between younger and older subjects (95). This is somewhat unexpected, since older subjects tend to sleep less, and with a more fragmented sleep pattern (96). However, there may be some individuals whose pressure does not fall during the night: in a study of 21 elderly hypertensives (mean age 70 years) Kobrin and colleagues found that 14 showed a normal diurnal rhythm of blood pressure, but 7 had similar levels of pressure throughout the 24-hour period (97). Interestingly, these patients all had evidence of cardiovascular disease, while this was true of less than half of the patients whose blood pressure showed a normal fall during the night. The variability of systolic pressure tends to increase with age, but not necessarily of diastolic pressure (94, 98).

The correlation between clinic and ambulatory 24-hour blood pressure may be less good in the elderly. Drayer and colleagues reported correlations of 0.69 and 0.71 (systolic and diastolic in patients aged less than 55 years, and 0.42 and 0.43 in those aged more than this) (95). Furthermore, the difference between clinic and ambulatory pressures may be greater in elderly than in young hypertensives according to some authors (98), but not others (99). This, of course, may result in a greater misclassification of such patients: in one study 42% of elderly subjects classified as hypertensive on the basis of their clinic pressures were normotensive on ambulatory monitoring (100).

Blacks

In Westernized societies the prevalence of hypertension is much higher in blacks than in whites (101), but despite extensive investigation the reason for this remains unexplained (102). The finding of a difference in the diurnal pattern of blood pressure between blacks and whites is of considerable interest. Therefore, Harshfield and colleagues performed ambulatory blood pressure recordings in 92 white and 107 black adolescents aged 10—15 years (103). The two groups had similar blood pressures while awake, but black children had significantly higher systolic and diastolic pressure while asleep (by about 5 mmHg). The same differences were not seen for heart rate. Similar findings have been reported for adults in studies performed in the United States using non-invasive monitors (104, 105). However, other studies, mostly performed in Europe and using invasive recordings, have failed to find a difference (106). That these differences are due to environmental factors rather than to the method of recording or genetic factors is suggested by the finding that blacks in Barbados, when studied using the same technique as in the United States, do show a normal nocturnal decline of blood pressure (107).

XV. WHITE COAT HYPERTENSION

For the clinician, perhaps the single most important application of ambulatory recording techniques is the detection of patients with 'white coat hypertension', which we have defined as a persistently elevated clinic pressure together with a nor-
normal daytime ambulatory pressure (108). The definitions of ‘elevated’ and ‘normal’ in this context are clearly quite arbitrary, and the prevalence of the condition will depend on the cutoff points used, as well as the population being studied, but in our own population is approximately 20%. Others have reported a prevalence of 38% (109) and 39% (110). The pressor effect of a physician in a clinic setting has been recognized for many years (111, 112), and may provoke a transient rise of pressure of as much as 30 or 40 mmHg. As a corollary of this, the correlation coefficient between physician-measured pressures and the average daytime ambulatory pressure is around 0.7 (113), which means that clinic pressures account for only about 50% of overall blood pressure variance.

In the office, the pressure recorded by the physician is typically consistently higher than the pressure recorded by a nurse or technician in the same physical setting (108), which in turn is likely to be higher than the pressure recorded by an automatic recorder with no observer present. In a study of 702 patients evaluated by ambulatory monitoring (44) whom we divided into 3 groups (58 normotensive, 578 with borderline hypertension, and 66 with established hypertension) on the basis of their clinic pressures, we found that in the normotensives approximately 60% of readings obtained during ambulatory monitoring were higher than the clinic level, while in the borderline and established hypertensives the corresponding figures were 40 and 20%, as shown in Figure 9.

The effects of interpersonal factors on blood pressure have been studied for many years, and indicate that persons in more authoritative positions are likely to provoke higher pressures: in a study of army recruits Reiser and colleagues (114) observed that when a captain took their blood pressure higher readings were obtained than when a private did.

The origins of the white coat effect are not well understood. It is observed in both young and old patients, of either sex, though with perhaps a slight preponderance in women (108, 115). It may be an important contributor to systolic hypertension of the elderly (116). Contrary to what might be expected, patients with white coat hypertension do not appear to be generally more anxious than others with sustained hypertension (110, 117, 118). Our working hypothesis to explain the phenomenon is that it begins as a manifestation of the defense response, which can produce a rise of pressure in anyone when the blood pressure is first taken. Normally, this habituates with repeated exposure, which accounts for the well-known tendency of clinic pressures to decline after multiple visits (119). In some patients, however, we hypothesize that this habituation does not take place, and the response may become permanent as a result of classical and cognitive conditioning. That this may occur has been well illustrated by a study in which 29 young men found to be hypertensive on an initial screening visit were randomly divided into two groups, one of which was informed that their pressures were high, while the other was not (120). On the second examination the first group’s blood pressure was 16/10 mmHg higher than the second group’s. Put another way, the patient who is told that his or her blood pressure is too high may become anxious on the second visit, so that the physician in the clinic setting acts as a conditioned stimulus, with the increased blood pressure as the conditioned response.

This view implies that the white coat effect should be specific to the clinic setting, and not simply a manifestation of generally increased blood pressure lability or reac-
Fig. 9. Proportion of ambulatory blood pressure readings that are higher than the average clinic readings for normal subjects, and patients with mild and established hypertension. Upper panel = systolic; lower panel = diastolic pressure. Reproduced with permission from Harshfield et al. (44).

tivity. Our own data, though limited, are in accord with this view, since our patients with white coat hypertension did not show an increased lability of pressure during ambulatory monitoring, and Floras and colleagues have obtained similar results (121).

The important practical question is whether such patients are at less risk of developing cardiovascular morbidity than others whose pressure is elevated both during clinic visits and at other times. As yet no conclusive answer can be given, but what evidence there is does indicate a lower risk. At least 3 studies have provided evidence that there is less target-organ damage in patients with white coat hypertension in comparison to those with essential hypertension (115, 121, 122). In one of these (122), White and colleagues showed that for the same level of clinic pressure, patients with white coat hypertension had less left ventricular hypertrophy and better left ventricular function than those with sustained hypertension. The only
published prognostic study, performed by Perloff and colleagues (123, 124), did not deal specifically with white coat hypertension, but did show that patients without target-organ damage whose ambulatory pressure was lower than their clinic pressures were at less risk than those in whom it was the same or higher.

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13. Ambulatory blood pressure measurement in the evaluation of antihypertensive drug effect

Eoin O’Brien, John Cox and Kevin O’Malley

The measurement of blood pressure whether with conventional sphygmomanometry, expensive and elaborate automated devices, non-invasive ambulatory systems, self-measuring devices or direct intra-arterial techniques is fraught with many potential errors. Far-reaching decisions have often been made, in relation to both patient management and scientific research, without due consideration being given to the limitations of the techniques available.

Why, one may ask, do editors of prestigious scientific medical journals demand (quite correctly) the exact methodology of, for example, an hormonal assay technique but disregard the detailed methodology of blood pressure measurement on which may depend the acceptance (or rejection) of an antihypertensive drug in clinical practice? Attention was first drawn to the failure of scientific journals to attach due importance to the methodology of blood pressure measurement in 1980 (1), and the situation has changed little a decade later (2).

Blood pressure measurement in the evaluation of antihypertensive drug efficacy may be conveniently divided into two broad categories. The first — isolated measurements — are those measurements which are essentially ‘casual’ in that they represent only a minute fraction of the 24-hour hemodynamic profile and are often recorded under rather artificial circumstances; included in this category are clinic measurements made with the mercury sphygmomanometer, and research measurements, made with, for example, the Hawksley random-zero sphygmomanometer and static semi-automated or automated devices. The second category — profile measurements — denotes those techniques, such as 24-hour ambulatory measurement and self-measurement, which attempt to determine blood pressure behavior over time and under varying circumstances reflecting more closely the subject’s environmental circumstances and provide an assessment of antihypertensive drug effect over time. So as to put in perspective the role of 24-hour ambulatory blood pressure measurement in the evaluation of antihypertensive drug treatment, it is necessary to first review the advantages and limitations of isolated measurements.
I. ISOLATED BLOOD PRESSURE MEASUREMENTS

Conventional sphygmomanometry

The procedure for measurement of blood pressure by conventional sphygmomanometry is replete with sources of potential error which may arise in the observer, the subject, the sphygmomanometer or in the overall application of the technique. It should go without saying that the problems that beset conventional sphygmomanometry in clinical practice (3) are also present in research studies of antihypertensive drugs. There are, however, certain aspects of the conventional measurement technique which are particularly relevant to the accuracy demanded in research.

Problems with sphygmomanometry in antihypertensive drug studies

The observer Perhaps the most neglected source of error is the observer. The successful outcome of the complex interaction that constitutes blood pressure measurement requires that the observer is competent in performing the technique of blood pressure measurement. In discussing observer competence we are faced with 3 problems: first, to identify the potential sources of observer error; second, to determine what constitutes adequate training; and, third, to devise a means of assessing the efficacy of that training.

In 1964, Geoffrey Rose and his colleagues classified observer error into 3 categories: systematic error, terminal digit preference and observer prejudice (4, 5). Various methods and techniques have been used to achieve greater accuracy in blood pressure measurement in clinical practice. These include direct instruction, manuals and booklets, audiotapes and video-films, all of which have been reviewed recently (3). In hypertension research it is desirable not only to train observers to a high level of accuracy, but it is also necessary to show that they have achieved this goal. An intensive observer training programme with the application of stringent accuracy criteria must therefore be followed by an assessment to ensure that the required standard is achieved (6).

The mercury sphygmomanometer The mercury sphygmomanometer is the simplest, most accurate and most economical device for the indirect measurement of blood pressure. There are, however, some empirical aspects of the mercury sphygmomanometer deserving of comment (2).

The state of sphygmomanometers in hospital use is far from satisfactory with as many as half being defective (7) and, though the situation is, hopefully considerably better in research, the state of the mercury sphygmomanometer should not be taken for granted, especially when, as may happen in studies of antihypertensive efficacy, a variety of hospital sphygmomanometers are used.

Of the many controversial issues in hypertension few can rival that of determining the optimal bladder dimensions for a particular arm circumference. A review of the sizable literature on the subject often serves to confuse rather than clarify (3). It is generally agreed that the width of the bladder is not as critical as the length provided bladder length is adequate and the bladder is not excessively narrow (8). For most
adult arms a width of 12–14 cm is adequate (9). The main argument centers on bladder length. The overwhelming opinion from the literature is for bladders with greater lengths (32–42 cm) so that the arm is encircled by the bladder in most subjects (3). The British Hypertension Society (10) and the British Standards Institution (11) have each decided to recommend only 3 cuffs for routine clinical use with the proviso that for very large arms care should be taken to ensure that the center of the bladder is placed over the brachial artery. In studies of antihypertensive drug efficacy it is imperative that the correct bladder is used and arm circumferences should be measured in all subjects.

It is assumed by most research workers that it is possible to support the arm in which measurement is being made at heart level by various strategies. Again when consideration is given to the care taken to ensure that the arm is accurately at heart level for intra-arterial measurement of blood pressure, the attitude to conventional measurement is put into none too flattering scientific perspective. If the arm in which measurement is being made is unsupported, as tends to happen if the subject is sitting or standing, isometric exercise is performed raising blood pressure and heart rate. Diastolic blood pressure may be raised by as much as 10% by having the arm extended and unsupported during blood pressure measurement (12). The effect of isometric exercise is greater in hypertensive patients and in those taking β-adrenoceptor blocking drugs (12). Dependency of the arm below heart level leads to an overestimation of systolic and diastolic pressures and raising the arm above heart level leads to underestimation of these pressures (13). The magnitude of this error can be as great as 10 mmHg for systolic and diastolic pressures. This source of error becomes especially important in the sitting and standing positions when the arm is likely to be dependent by the subject’s side. However, even in the supine position an error is introduced if the arm is not supported at heart level (14). In studies of antihypertensive drug efficacy, and indeed in all research in which conventional measurement is used, a support device should be used to ensure that the arm is both supported and at heart level.

**Research sphygmomanometry**

Blood pressure measurement by an observer using a standard mercury sphygmomanometer and stethoscope is subject to observer prejudice and terminal digit preference which can introduce error that is unacceptable for research work. Two devices have been designed specifically for research use — the Hawksley random-zero sphygmomanometer, which reduces observer bias, and the London School of Hygiene and Tropical Medicine sphygmomanometer, which reduces both observer bias and terminal digit preference. The latter device, which is inaccurate due to a calibration error, is no longer available (15). The random-zero sphygmomanometer (Hawksley), which reduces observer prejudice but not digit preference has been the instrument of choice for epidemiological and research studies (16). However, recent studies have shown that the instrument systematically gives lower readings than the standard mercury sphygmomanometer and it can no longer be recommended for research and epidemiological studies (17).
Automated and semi-automated sphygmomanometry

One consequence of the increased interest in blood pressure measurement has been the creation of a large market for automated and semi-automated devices for static blood pressure measurement. In recent years the number of devices available commercially has risen rapidly, but most have been shown to be less accurate than the mercury sphygmomanometer (18), though some have been found to be satisfactory (19). At present there is no obligation on manufacturers to comply with the few recommended standards that are available (20). There is no standard for automated blood pressure measuring devices in the United Kingdom. In the United States, the Association for the Advancement of Medical Instrumentation (AAMI), has produced a detailed standard for semi-automated and automated devices (21) and the British Hypertension Society has published a protocol for evaluating automated devices with special reference to ambulatory measuring systems (22).

The availability of an automated device validated independently by present-day criteria would be a distinct advantage in the evaluation of antihypertensive drug efficacy. Such a device would eliminate errors of interpretation, reduce or eliminate both observer prejudice and terminal digit preference, obviate the necessity for elaborate observer training and assessment as described above and possibly also reduce the white coat effect. Moreover, if accurate semi-automated devices were available self-measurement of blood pressure could be employed to reduce observer error by removing the interaction between subject and observer. At the time of writing we do not know of an automated device which has been shown conclusively to be as accurate as the mercury sphygmomanometer for the measurement of blood pressure. The advent of such a device is eagerly awaited.

Disadvantages of isolated measurements in antihypertensive drug assessment

Quite apart from the methodological problems already discussed, isolated measurements have a number of inherent features that greatly affect application of these techniques to antihypertensive drug studies.

Clinic blood pressures vary greatly (23) and repeated measurements improve the reliability of the conventional technique (24). One important consequence of this variability is that relatively large numbers of patients must be studied to demonstrate a clinically significant difference of, say, 5 mmHg between antihypertensive drugs (25).

The problem of regression to the mean whereby successive measurements give lower readings in hypertensive patients (or higher readings in subjects with low blood pressure) has bedevilled studies of antihypertensive drug efficacy necessitating long run-in periods (26). Regression to the mean has the potential for increasing the number of responders in antihypertensive drug studies, especially in patients with higher levels of blood pressure, such as the elderly, and a control placebo group is, therefore, necessary to permit assessment of the number of true responders to the drug.

Anxiety raises blood pressure substantially. The defence or alarm reaction is a rise in blood pressure associated with blood pressure measurement (27). This increase in blood pressure may subside once the subject becomes accustomed to the pro-
cedure and the observer, but in many subjects blood pressure is always higher when measured by doctors, and to a lesser degree by nurses — so-called 'white coat hypertension' (28). In this regard it is important to note that the alarm reaction to the process of blood pressure measurement may persist after several visits.

The presence of a placebo response with conventional measurement makes it mandatory to include a placebo control in studies of antihypertensive drug efficacy (29).

In concluding this review of conventional sphygmomanometry in the evaluation of antihypertensive drug efficacy, it is apparent that the limitations of isolated measurements are such that serious consideration must be given to their place in such studies. If, as is likely, conventional sphygmomanometry continues to be used, the technique must be accorded the care and attention to detail that is demanded of other scientific measurements, having regard to all the imperfections inherent in the method and its application.

II. PROFILE BLOOD PRESSURE MEASUREMENTS

Twenty-four-hour ambulatory measurement

Ambulatory blood pressure measurement over 24 hours has given new insights into blood pressure behavior and is bringing about such a reappraisal of previously held concepts on hypertension that diagnostic and therapeutic decisions in practice are being critically evaluated (30). Similarly, in clinical research, 24-hour ambulatory blood pressure measurement is providing exciting possibilities for the study of blood pressure behavior, especially in the assessment of antihypertensive drug efficacy. The advantages of 24-hour ambulatory measurement over conventional techniques may be considered in relation to the ability of the technique to detect drug effect that may not be evident with conventional measurement, to provide information on the duration of antihypertensive drug effect, its role in improving the design of studies of antihypertensive drug efficacy, and the ability of the technique to demonstrate the effect of drugs on nocturnal blood pressure and the potential problems associated with excessive lowering of blood pressure. It is our opinion that the use of invasive intra-arterial techniques for the measurement of ambulatory blood pressure in the evaluation of antihypertensive drugs is ethically acceptable in only exceptional circumstances and should be strictly confined to those few centers with a long experience and well-proven expertise in the technique; the discussion in this paper is, therefore, confined to non-invasive methods.

As with all innovative techniques there comes the need for new terms to denote new phenomena. We have previously given to those hypertensive patients with a substantial nocturnal fall in blood pressure the descriptive title of 'dippers' to distinguish them from those much fewer patients who do not reduce night-time pressure — the 'non-dippers' (31) and the terms seem to have found acceptance (32). We now find ourselves in need of another descriptive term. White and his colleagues have demonstrated that blood pressure 'load', as indicated by the percentage of systolic or diastolic measurements above normal during a 24-hour period, is a good predictor of left ventricular enlargement (33). By the same token we need to be able
to denote changes in the other direction, namely excessive reductions in blood pressure outside the lower limits of the normal range. We propose, therefore, the concept of load to indicate increases in blood pressure above the upper limits of normality and leese (meaning literally the release or relaxation) to denote a reduction in blood pressure below the lower limits (34). However, before discussing such concepts it is important to define the normal 24-hour blood pressure.

**Normal 24-hour blood pressure**

Using the World Health Organisation (WHO) cut-off level of 160/95 mmHg made life relatively simple in that the number of readings and the circumstances of measurement for entry to a study had only to be decided and the efficacy or otherwise of an antihypertensive drug could then be evaluated. If ambulatory blood pressure levels are now to be used for entry criteria to drug studies, we are faced with a more daunting task at the very outset than was ever the case previously. However, the subsequent rewards may be considerable.

By considering the mean and two standard deviations for daytime and night-time pressures in 815 men and women aged 17 – 80 years it is evident that there are considerable differences between young and old and that men have higher pressures than women for both daytime and night-time pressures (35); to apply the levels of one to the other would be quite inappropriate. If we wished, for example, to study the efficacy of a drug in both sexes (as is usually the case) and in subjects below the age of 65 (as is commonly the case) it is evident that entry without consideration of the difference in level between either men and women and between young and old would have serious implications in terms of simply deciding who was hypertensive and who was not. To take a specific example: a study might have a predetermined entry mean daytime blood pressure of ≥ 140/85 mmHg to which a 20-year-old woman might be entered with a mean daytime pressure of 142/90 mmHg, which in her case is frankly hypertensive, the upper limit of her pressure as judged by the mean plus two standard deviations being 133/87 mmHg, and she comfortably fulfills the entry criteria; a 50-year-old man with the same mean daytime pressure would also fulfill the entry criteria but would not be hypertensive for his age and sex if two standard deviations above the mean is taken as the upper limit of normality (156/103 mmHg). This aspect of antihypertensive drug efficacy has been neglected in the face of our scientific obduracy in being prepared to ignore the epidemiological evidence that blood pressure measured conventionally or with more elaborate techniques varies with age and according to sex. The difficulties in overcoming the problem are not as great as might first appear to be the case. With a number of population studies attempting to determine the normal reference values for 24-hour pressure and with one large study already completed (35) the reference levels for different groups will soon be evident. Furthermore, as the evidence accumulates showing that 24-hour pressures are superior to conventional measurement in predicting end-organ effect (32, 36, 37), the justification for making entry decisions on 24-hour rather than office blood pressure becomes stronger. If entry blood pressures are based on, say, daytime pressures according to age and sex, the recruitment of patients will be facilitated because it may become justifiable to enter
patients with blood pressures that would be regarded as being within the normal range relevant to WHO criteria.

Detection of antihypertensive drug effect

One of the most surprising aspects of research into the efficacy of antihypertensive drugs is the readiness with which a blood-pressure-lowering effect observed at one moment in the 24-hour cycle, often without reference to the time of drug administration, has been taken to indicate therapeutic efficacy throughout the day. With the increasing use of new formulations of drugs that permit once and twice daily dosage (38), it is now more important than ever to be able to assess the pattern as well as the duration of drug effect.

For the past decade it has been our policy to incorporate ambulatory measurement into our study protocols of blood-pressure-lowering drugs (38). Initially, we used daytime ambulatory measurement in double-blind, cross-over studies of drug efficacy. From the results of these and other similar studies a number of patterns emerge. In some studies conventional clinic sphygmomanometry is vindicated, in that a fall in clinic blood pressure is confirmed by ambulatory measurement of daytime pressure (38). However, the ambulatory technique demonstrates what can never be shown by clinic measurement, namely the pattern of antihypertensive drug effect over time. In other studies conventional clinic blood pressure measurement may fail to detect a blood-pressure-lowering effect demonstrated by ambulatory measurement (38). In these studies clinic blood pressure may have been performed before the onset of antihypertensive drug effect. Finally, there are many studies showing statistically significant reductions in clinic blood pressure which either are not confirmed by ambulatory measurement (38) or are shown to be present only for a brief period coinciding with the observed clinic reduction (39, 40). Of considerable practical importance is the fact that many preparations which would have been declared quite efficacious blood-pressure-lowering agents by conventional measurement were shown by ambulatory measurement to have a far less impressive pattern of activity.

Some of these discrepancies between the two techniques may be explained simply by the time of onset and the duration of action of a particular drug in relation to the time and frequency of measurement, but there is evidence that the explanation is not always this simple. It is possible that the mechanism of lowering blood pressure in the clinic (and the amount of drug needed to do so) is different from that operating in ambulatory circumstances (38).

Duration of antihypertensive drug effect

Ambulatory measurement provides what was only previously obtainable with direct invasive intra-arterial measurement — an assessment of antihypertensive drug effect over 24 or 48 hours. Until recently interest in this aspect of 24-hour measurement centered on the desirability of being able to demonstrate that a drug was efficacious for the appropriate period related to dosing. This facility proved useful in demonstrating that drugs possessed or did not possess the duration of action claimed for them. With recent interest in the potential danger of excessive lowering of
blood pressure with antihypertensive medication (41), the role of 24-hour blood pressure monitoring in detecting such reduction in pressure, especially during the nocturnal period, may prove to be an important one.

Design of antihypertensive drug efficacy studies

*White coat* responders  Anxiety raises blood pressure substantially. The defence or alarm reaction is a rise in blood pressure associated with blood pressure measurement (27). This increase in blood pressure may subside once the subject becomes accustomed to the procedure and the circumstances in which it is carried out, but in many subjects blood pressure is always higher when measured by doctors, and to a lesser degree by nurses — so-called 'white coat hypertension' (28). In this regard it is important to note that the alarm reaction to the process of blood pressure measurement may persist after several visits. The white coat phenomenon, now a well-recognized entity, can only be characterized by ambulatory techniques of measurement.

Pickering and his colleagues have shown that more than 20% of patients with borderline hypertension diagnosed by clinic measurement have normal daytime ambulatory blood pressure (28). However, it is important to enter a word of caution about definition of hypertension at this point. We, in common with others, have tended to apply the WHO cut-off point for hypertension to ambulatory measurement. For example, using a cut-off point of \( \geq 160/95 \) mmHg, 89% of our patients would have been diagnosed hypertensive by the family practitioner using conventional measurement whereas this figure would have fallen to 46% with non-invasive ambulatory measurement (42); but these comparisons were being made in the days before reference values for ambulatory measurement were available. We must now relate our management decisions to the normal ambulatory levels of pressure and not to the long-serving WHO criteria, and this is especially so in judging the efficacy of antihypertensive drugs.

If patients with white coat hypertension are included in a study, as is often the case when patients are recruited by conventional clinic measurement, we might expect as many as one-fifth of these patients not to have sustained hypertension (38) and to be, therefore, unsuitable for the study. Moreover, patients with white coat hypertension may respond differently to antihypertensive drugs and develop more side-effects (43).

Placebo response  What exactly is the placebo effect or response? The terms 'effect' and 'response' are generally used synonymously, though the words have rather different meanings. 'Placebo effect' when interpreted literally implies that the placebo medication has in itself the potential for lowering blood pressure, whereas 'placebo response' might be taken to mean that the administration of a placebo is associated with a reduction in blood pressure and does not necessarily imply that the response is due to some property of the placebo. It is, therefore, a better term because it allows the blood pressure lowering associated with placebo administration to be attributed to the circumstances of measurement rather than to the placebo itself.

Whatever terminology is used, there is little doubt but that the phenomenon does
exist (26) and has been demonstrated in most hypertensive patients (29), though there have been studies in which a placebo response was not observed (44). The placebo response may be an artefact of clinic blood pressure measurement associated with the inherent variability of arterial pressure, errors of measurement, regression to the mean and increasing familiarity of the patient with the clinic procedure, rather than being due to the placebo itself (44). Several clinic measurements are required before these factors are overcome and the true level of blood pressure can be ascertained (44). As a consequence placebo control in studies dependent on isolated measurements is deemed mandatory (29), though the inclusion of a placebo may lead to underestimation of the efficacy of an antihypertensive drug (44).

An important difference between conventional and ambulatory blood pressure measurement is the absence of a placebo response with the latter, whether measurement is invasive (44) or non-invasive (45–48), though one study demonstrated a small but weakly statistically significant placebo response with daytime ambulatory measurement (49). We have recently confirmed that the placebo response is not present with non-invasive 24-hour measurement (50).

The absence of a placebo effect with non-invasive ambulatory measurement allows the opportunity of greatly simplifying the design and conduct of efficacy studies of antihypertensive drugs. For example, many investigators employ a randomized placebo-controlled cross-over design, on the basis that a comparison between treatments in the same subject is more precise and requires fewer subjects than a comparison between subjects. In such studies, a wash-out period before patients cross-over treatments is recommended to reduce the possibility of a treatment-period interaction (51). However, as there is no placebo effect with ambulatory blood pressure monitoring, measurement performed before and repeated at the end of the treatment period would suffice, making the cross-over design with its risks of carry-over effects and the need for prolonged placebo administration unnecessary. In fact, this approach has been adopted by Raftery and his colleagues for the last decade using direct intra-arterial ambulatory blood pressure measurement (52).

Placebo may also be used in a run-in phase of antihypertensive drug evaluation to determine which patients remain, as it were, genuinely hypertensive. Many patients entering a placebo phase of a study on the basis of being diagnosed mild to moderate hypertensives by clinic blood pressure measurement will fail to qualify for formal admission to the study because their blood pressure no longer meets the admission criteria. A placebo-controlled phase is included, therefore, in some studies to exclude normotensives and detect truly hypertensive patients. A recent study by Gradman and colleagues has shown that about a quarter of patients designated hypertensive in this way had normal ambulatory blood pressures and that the use of a placebo-controlled run-in phase did not assure the selection of a genuine hypertensive group (53).

Regression to the mean Regression to the mean has the potential for increasing the number of responders in antihypertensive drug studies, especially in patients with higher levels of blood pressure, such as the elderly, and a control placebo group is, therefore, necessary to permit assessment of the number of true responders to the drug (26). Ambulatory measurement does not regress to the mean, by which is
meant that subjects with high pressures do not exhibit a fall in pressure and that those in whom pressures are low do not show a tendency to raise their pressure with repeated measurement (54). This being so, ambulatory measurement may further enhance the likelihood of entering into a study only those patients with genuine hypertension.

*Ambulatory measurement and sample size*  It is becoming more difficult to recruit patients for studies of antihypertensive drug efficacy. This may be attributed to a number of factors, some of which cannot, at the time of writing, be substantiated by factual documentation and are little more than impressions. There are first of all the ethical restraints, which are quite correctly stricter and more perspicacious than in the past. However laudable this may be, the reality is that efficacy studies are becoming more difficult to design and this trend is likely to continue. There is also the impression that hypertension has become a milder illness than hithertofore and in many societies, such as in Ireland where the standard of primary medical care is high, the number of patients presenting at our blood pressure clinic with severe hypertension is decreasing steadily. Indeed, accelerated hypertension has become a clinical rarity. We are being left, therefore, with patients designated as mild hypertensives. Obviously the anticipated reduction in blood pressure with drugs in such patients has to be modest and with this realization comes the problem of detecting a blood-pressure-lowering effect in small numbers, a topic on which Conway and his colleagues have made some interesting observations (47, 55). To this must be added the reality of how difficult it is to actually find patients who fulfill the criteria for entry after the run-in or wash-out phase of a study. In our experience it may be relatively easy to recruit patients who appear to be suitable, but when it comes to entry only 30–50% of those originally identified remain eligible for entry. This rather sceptical but, none the less, realistic view of patient recruitment contrasts with the recently stated thoughts of the Food and Drug Administration which believes that ‘hypertension is widely prevalent, making study patients comparatively easy to find’ (56).

Twenty-four-hour blood pressure measurements improve the precision with which blood pressure reduction can be quantified (48, 54). Conway and his colleagues have shown that in 100 hypertensive patients the standard deviation of differences (SDD) for clinic measurements falls progressively from 12.6 mmHg as the number of readings is increased to 6.5 mmHg for 20 measurements during the day. As the SDD falls, so too does the number of subjects required for a study. Conway has estimated that with the SDD equal to 8.1/5.6 mmHg, as is the case with daytime ambulatory recordings, it should be possible to detect that two agents differ from each other by 8/5 mmHg with approximately 16 subjects using a cross-over design (47). Put another way, halving the standard deviation of the difference between readings about doubles the precision of the trial, thereby permitting a fourfold reduction in the number of subjects required to achieve an accurate result. For example, to detect a 5 mmHg difference in diastolic blood pressure, halving the SDD, as might be possible with ambulatory measurement, would reduce the numbers of subjects needed in a parallel group trial from 250 to 67 and for a cross-over trial from 61 to 16 (57).

This interesting concept, which has far-reaching implications for the design of
antihypertensive studies, needs to be carefully evaluated in the light of growing knowledge with ambulatory techniques. We have attempted to apply this approach retrospectively to studies of antihypertensive drug efficacy which we have conducted. A reduction in the SDD for systolic and diastolic pressure with ambulatory measurement was seen in only two studies, one involving nicardipine (58) and the other, ketanserin (40), whereas in the other studies the SDD increased for both systolic and diastolic pressures with ambulatory measurement. In a study in which placebo rather than drug was given, the reduction in SDD for diastolic pressure is similar to that noted by Conway who also used placebo and it may be that the effect of antihypertensive drugs on the SDD is different from that of placebo. Other factors, such as the degree of activity during ambulatory recording, age and lability of blood pressure, may also contribute to variable effect of drugs on the SDD. Whatever the explanation, this potentially important aspect of antihypertensive drug evaluation needs further study.

Nocturnal blood pressure, load and leese

There is now evidence that hypertensive patients whose treated blood pressures are lowest have the highest incidence of myocardial infarction (59, 60). For this reason we must now direct our attention, not only to the efficacy of blood pressure reduction in studies of antihypertensive drugs, but also to the magnitude of this reduction, the leese of pressure, as we have termed it. This may be especially relevant following the suggestion that both a large and small reduction of blood pressure, especially diastolic pressure, may be associated with a higher incidence of myocardial infarction than a moderate fall (60). Reviewing the evidence that lowering blood pressure may increase the risk of myocardial infarction has led Berglund to make the recommendation that until further evidence is available clinic diastolic blood pressure should not be reduced below 85 mmHg (41), but he did not give consideration to the potential effects of blood pressure reduction at different times throughout the 24-hour cycle.

There is some evidence that hypertensive patients who do not have a nocturnal fall in blood pressure (non-dippers) are at greater risk than the majority who show a substantial reduction in nocturnal blood pressure (dippers) (31, 32, 36). Moreover, it has been recently demonstrated that end-organ damage, as judged by left ventricular size, is more marked in non-dippers than in dippers (36). The possibility also exists that antihypertensive drugs with a prolonged duration of effect, or administered frequently, may cause a profound reduction in nocturnal blood pressure in some patients, and that this might lead to myocardial ischemia and infarction (61). While the therapeutic and prognostic implications of these findings require further evaluation, they provide cogent evidence in favor of assessing the effects of antihypertensive therapy on sleeping blood pressure.

Effect of different drugs on circadian pattern

Because of the potential importance of diurnal blood pressure rhythmicity, we analyzed retrospectively 2859 24-hour ambulatory records obtained over a 3-year period to determine if currently used antihypertensive drugs had different effects on
the 24-hour circadian pattern (74). The most important point to emerge from this analysis was that hypertensives on angiotensin-converting-enzyme (ACE) inhibitors had markedly accentuated systolic and diastolic dipping patterns compared to untreated hypertensives and patients on beta-blockers. Hypertensive patients treated with beta-blockers, calcium antagonists or diuretics had similar diastolic and systolic dipping patterns to the untreated groups. Whatever the explanation for these varying effects of different groups of antihypertensive drugs, which need to be assessed in more detail in prospective studies, the fact that some drugs may accentuate nocturnal dipping, that others may blunt the normal nocturnal fall in blood pressure and that others have no effect on diurnal rhythmicity, raises important questions in assessing antihypertensive drug effect and in choosing a drug for an individual patient. As was once said so truely of hypertension — the only way of diagnosing the condition is by measuring the blood pressure — so too with nocturnal dipping status the only means of characterizing its magnitude is by performing 24-hour blood pressure measurement.

**Home measurement**

Self-measurement of blood pressure is another technique capable of providing *profile measurements*. The usefulness of self-measurement of blood pressure in the assessment of the effects of therapy has been shown in several studies (38) and the topic is reviewed in Chapter 5. However, the technique has the disadvantages of being dependent on the ability of the subject to measure his or her blood pressure, of necessitating training of the subject and of being susceptible to observer bias and fabrication of results, and the muscular activity required to inflate the cuff has been shown to increase systolic blood pressure by more than 10 mmHg (63). Also, the patient’s over-reaction to the normal fluctuations in blood pressure associated with daily living may cause psychological distress and affect the results in an unpredictable fashion (64). The technique is further limited in that it is dependent on the subject’s participation and cannot, therefore, give multiple readings during the day or any assessment of nocturnal pressure.

Against these disadvantages must be weighed the cost of ambulatory blood pressure measurement and the fact that 24-hour monitoring is a relatively intrusive procedure, which is readily tolerated as an occasional investigation but is not always received warmly as a repeated procedure by subjects participating in a study of antihypertensive efficacy when as many as 3 or 4 24-hour assessments may be required in a relatively short space of time. It may be that in these circumstances and in the clinical management of hypertension, self-measurement of blood pressure may survive as a means of obtaining limited information on blood pressure behavior in the home environment (65).

**III. CONCLUSIONS**

The benefits of ambulatory blood pressure monitoring in the assessment of the efficacy of drug treatment are now well established, which is not to say that considerable study and, perhaps more importantly, deliberation on the research amas-
sed over the past decade, is not now needed. Conventional clinic measurement is influenced by many factors which limit the applicability of this technique for research into drug efficacy, but, more importantly, clinic measurement cannot provide a comprehensive assessment of duration of effect, or of the effect of antihypertensive drugs on sleeping pressure. Home measurement of blood pressure, though valuable in assessing blood pressure control in clinical practice, is not as informative as ambulatory blood pressure measurement and cannot provide nocturnal pressures.

As non-invasive ambulatory blood pressure is free of any placebo effect, it is now possible to consider efficacy studies which need not have a placebo phase, thus greatly simplifying the design of antihypertensive studies. Moreover, the provision of considerably more observations than is possible with clinic measurement, by reducing within-subject variability and greatly increasing the power of studies, may reduce substantially the numbers of patients needed for such studies.

Opponents to this line of reasoning will argue, with what should be diminishing conviction, that there is not sufficient prognostic data to permit acceptance of the view that, on the one hand, inadequate reduction of 24-hour blood pressure by antihypertensive medication may be disadvantageous to our patients or that, on the other, excessive reduction may be possibly more deleterious, and that we should base our decisions on the time-honored and reliable prognostic data from conventional clinic blood pressure. Whatever truth there is in this attitude, the indirect evidence deriving from end-organ studies, as distinct from long-term morbidity and mortality studies (which will take many years to perform at considerable cost), is such, and the incidental benefits of the technique are so helpful in practice, that it cannot but achieve the popularity which is now becoming a reality. From the scientific viewpoint it behoves us to utilize the technique to obtain a fuller understanding of the patterns of drug-induced lowering of blood pressure than was ever possible with conventional clinic measurement.

The time has surely come when studies of antihypertensive drug efficacy which do not assess blood pressure over 24 hours should no longer be acceptable.

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14. Ambulatory blood pressure in assessing the cardiac impact and prognosis of hypertension

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Although hypertension is an established risk factor for cardiovascular morbidity (1–3), blood pressure is only weakly related to the likelihood of complications in individual patients with mild to moderate hypertension (4). Furthermore, wide variability exists among subjects and between different types of hypertension, at any given level of blood pressure, in the prevalence and severity of such target organ manifestations as left ventricular (LV) hypertrophy or vascular damage. One possible explanation for this unsatisfactory situation is that clinically measured arterial pressure may be unrepresentative of the true hemodynamic overload imposed by hypertension.

In 1966 Solokow and Perloff reported that target organ effects of hypertension, assessed by funduscopic examination and indirect techniques such as the electrocardiogram, were more closely related to ambulatory blood pressure (measured by patient-activated recorders) than to casual pressure measurements (5). This finding has been subsequently confirmed by other investigators (6–7). More recently, numerous studies have shown that pressure determined by ambulatory monitor or during physical exercise is a better predictor than casual blood pressure of LV mass and geometry measured directly by echocardiography (6, 8–21), and two groups of investigators have found ambulatory pressures to add to casual pressures in predicting the prognosis of hypertensive patients (22–24).

These observations have potentially fundamental implications for how hypertension is diagnosed and its severity judged. Accordingly in this chapter we will examine: (a) the anatomic accuracy and prognostic significance of echocardiographic LV mass measurement as an indicator of hypertensive heart disease; (b) the relation between measurements of blood pressure by ambulatory monitor and echocardiographic indices of LV structure; (c) the relation of LV mass to blood pressure during physical exercise; (d) the relation of ambulatory blood pressure to prognosis in hypertension; and (e) the clinical and theoretical implications of these findings.
I. LEFT VENTRICULAR MASS AS A BIOASSAY FOR PRECLINICAL HYPERTENSIVE HEART DISEASE

Anatomic validation of echocardiographic left ventricular mass

Echocardiography permits non-invasive measurement of LV wall thicknesses and cavity size from which it is possible to calculate LV muscle mass (25 – 29). The first and simplest anatomically-validated method used end-diastolic M-mode echocardiographic measurements of interventricular septal thickness (IVS), LV internal dimension (LVID) and posterior wall thickness (PWT) by the Penn convention in a regression formula (25, 29):

\[
LV\ mass = 1.04 \left[ (IVS + LVID + PWT)^3 - LVID^3 \right] - 13.6g
\]

LV mass estimates by this method were closely related to ventricular weight at autopsy in sequential studies of 34 and 52 patients \( r = 0.96 \) and \( r = 0.92 \), both \( P < 0.001 \) (25, 29).

Because M-mode echocardiographic measurements are usually made using the leading-edge methodology recommended by the American Society of Echocardiography (ASE) (30) we also examined the anatomic accuracy of LV mass estimated from ASE measurements. We found, as did Woythaler and colleagues (27), that anatomic LV mass was overestimated, by a mean of nearly 20%, when end-diastolic ASE measurements were used in the cube function formula (29, 31). This error can be corrected by a simple regression equation (29):

\[
LV\ mass_{ASE} = 0.8 \left[ 1.04(IVS + LVID + PWT)^3 - LVID^3 \right] + 0.6g
\]

Results by this method were closely related to autopsy values \( r = 90, P < 0.001 \).

Two-dimensional (2-D) echocardiography visualizes cardiac structures more completely than M-mode echocardiography, allowing planimetry of cross-sectional areas and measurements of the length of specified axes through the left ventricle. These advantages have been utilized in 2-D echocardiographic methods of LV mass determination that are similar or slightly superior to M-mode methods in anatomic accuracy (25, 28, 32). While their computational difficulty has to date limited the use of 2-D methods, they may be preferable when LV geometry is distorted, as by myocardial infarction (26), or when extremely high levels of reproducibility are needed in serial comparison studies (33). Equivalent or possibly even higher accuracy in measurement of LV mass can be obtained by use of magnetic resonance imaging (34) or cine computed tomography (35), albeit with greater cost and inconvenience due to the use of expensive, immobile equipment.

Prognostic significance of echocardiographic left ventricular hypertrophy

To determine the prognostic significance of an abnormality such as LV hypertrophy, it is necessary to identify partition values to separate abnormal from normal with high specificity, to perform longitudinal studies to verify that abnormal values predict an adverse prognosis, and to determine that this predictive value is indepen-
Fig. 1. In a longitudinal study of 140 men with initially uncomplicated essential hypertension, the incidence of cardiovascular morbid events was approximately 4-fold higher in those with than those without increased left ventricular mass measured echocardiographically. Adapted from data of Casale et al. (51).

dent of blood pressure or other conventional risk factors. This has been accomplished for echocardiographic LV mass, as several groups of investigators have developed similar sex-specific upper limits of normal LV mass, which are most useful when indexed for a measure of body size such as body surface area or height (36 – 40). LV mass exceeds these normal limits in variable proportions of patients with established hypertension, ranging from as low as 19% among employed adults with mild essential hypertension to over 80% among hospitalized patients with moderate to severe hypertension (40 – 47). These rates contrast with prevalences of electrocardiographic LV hypertrophy of 5% or less among average hypertensives (41), a difference that reflects the low sensitivity of the electrocardiogram for this purpose (48). In fact, data from Framingham show that standard ECG criteria detect fewer than 7% of adults with increased LV mass in the general population (49, 50).

To determine the prognostic significance of echocardiographic LV hypertrophy we performed a 5-year follow-up study of 140 men with initially uncomplicated, generally mild, essential hypertension (51). Patients whose baseline LV mass exceeded 125 g/m² were considered to have LV hypertrophy, based on the distribution of LV mass values in a separate study of normotensive and hypertensive employed adults (45). No difference in age, blood pressure, or the prevalence of cigarette smoking or high cholesterol levels existed between the 29 men (20%) with and the 111 (80%) without LV hypertrophy (51). During follow-up, one or more 'hard' morbid events (cardiac death, myocardial infarction, stroke, or angina pectoris requiring coronary bypass surgery) occurred in 7 or 24% of the men with LV hypertrophy and 7 or 6% of the men without LV hypertrophy (P < 0.01). This resulted in a roughly 4-fold difference in the incidence of morbid events (Fig. 1). Multivariate analysis revealed that echocardiographic LV mass, considered as a con-
Continuous variable, was a stronger independent predictor of complications than either systolic or diastolic blood pressure or age (51).

Subsequent studies have confirmed and extended these findings by demonstrating that echocardiographically measured LV mass is a strong predictor, independent of casual blood pressure or other risk factors, of cardiovascular morbidity and mortality among men and women with uncomplicated essential hypertension (52–55) and initially healthy middle-aged and elderly adults in the general population (56, 57). In the Framingham population sample, the relation between LV mass and risk was more evident among subjects with hypertension or hypercholesterolemia than among those without these risk factors (Fig. 2). In our experience echocardiographic measurement of the LV wall thickness/radius ratio (relative wall thickness) has aided in further stratification of risk with the highest incidence of death and non-fatal events occurring in patients with increased values of both LV mass and relative wall thickness (concentric LV hypertrophy) (58).

Echocardiographic LV mass measurements have also been shown to be a strong predictor of mortality following myocardial infarction, independent of the severity of coronary artery disease, in a group of patients most of whom were hypertensive (59, 60). Similarly, high LV mass predicted two- to fourfold increases in the risk of death among patients on hemodialysis for chronic renal failure, a group with a high

**Fig. 2.** Four-year incidence (per 100 subjects) of initial coronary heart disease events according to quartile of left ventricular mass/height in women (left panel) and men (right panel). *Top:* Rates are indicated for subjects with hypertension (solid bars) and for normotensive subjects (striped bars). *Bottom:* Rates are stratified by ratio of total/HDL cholesterol (striped bars = ratio < 4.5, solid bars = ratio ≥ 4.5). Increasing levels of left ventricular mass predict risk, with positive dose–response relations, in subjects with hypertension or an adverse lipid profile better than in subjects without these risk factors. Reproduced from Levy et al. (56) by permission of the American College of Physicians.
prevalence of hypertension (61). These results indicate that echocardiographic LV mass is a useful bioassay for prognostically significant effects of hypertension — either alone or in association with other diseases — on cardiovascular structure.

II. RELATION BETWEEN AMBULATORY BLOOD PRESSURE AND LEFT VENTRICULAR STRUCTURE

With the development of invasive (62, 63) and non-invasive (64) methods for ambulatory measurement of blood pressure, it became clear that blood pressure varies widely during normal activity and that both its average level and its variability may not be accurately revealed by casual readings. This suggested that the level of blood pressure throughout the 24-hour day, or during some component thereof, might be more important than clinically measured blood pressure as a determinant of both cardiovascular structure and clinical prognosis in systemic hypertension. Available data tend to support a particularly important role of ambulatory blood pressure with regard to cardiac structure (6, 8—18) as well as clinical prognosis (22–24). Because most research studies and virtually all clinical evaluations are currently performed with non-invasive ambulatory monitors, it will be assumed below that this is the case unless the use of intra-arterial recordings is specifically mentioned.

Systolic blood pressure

As may be seen in Table 1, LV muscle mass or wall thicknesses have been more closely related to 24-hour systolic blood pressure than to casual systolic blood pressure in each of the 11 studies in which both correlations were reported (6, 8–10, 13–18, 65). These differences in favor of ambulatory pressure measurements become even more striking when one calculates the coefficient of determination ($r^2$) as an index of the proportion of variability in ventricular mass that can be attributed to each measure of blood pressure (Fig. 3).

Time of day and activity

Analyses have been undertaken of the relations of LV muscle mass to several components of 24-hour blood pressure. Several studies have shown that daytime pressures were more closely correlated than sleep recordings with measures of LV anatomy (8–10). Self-recorded pressures at home during the daytime have also been shown to be more closely related to LV geometry than were physician measurements (66). One possible explanation for this observation is that the nocturnal depressor response in patients with uncomplicated essential hypertension tends to be proportional to daytime pressures, thus reducing the range of blood pressures at night compared to the daytime (J.M. Mallion, M.D., personal communication). Conversely, blunting of the nocturnal depressor response, a characteristic of more severe forms of hypertension, has been suggested by Smith and colleagues (67) to be associated with higher levels of LV mass among patients at any level of daytime blood pressure. The finding by Verdecchia and colleagues (18) that LV mass and relative wall thickness were slightly more closely related to ambulatory pressures be-
### TABLE 1. Relation between ambulatory systolic blood pressure and left ventricular structure

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Blood pressure status</th>
<th>Measure of LV structure</th>
<th>Correlation between systolic blood pressure and LV structure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Casual BP</td>
</tr>
<tr>
<td>Rowlands (8)</td>
<td>50</td>
<td>High</td>
<td>LV mass index</td>
<td>0.45***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LV mass index</td>
<td>0.55</td>
</tr>
<tr>
<td>Drayer (9)</td>
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<td>High</td>
<td>LV mass index</td>
<td>0.24*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RWTd</td>
<td>0.24*</td>
</tr>
<tr>
<td>Devereux (10)</td>
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<td>Normal and high</td>
<td>LV mass index</td>
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</tr>
<tr>
<td>Dimitriou (11)</td>
<td>26</td>
<td></td>
<td>IVSd</td>
<td>to</td>
</tr>
<tr>
<td>Lattuada (12)</td>
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<td>IVSd</td>
<td>0.23</td>
</tr>
<tr>
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</tr>
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<td>DeGaudemaras (13)</td>
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<td>White (15)</td>
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<td>Normal</td>
<td>PWTd</td>
<td>0.10</td>
</tr>
<tr>
<td>Prisant (17)</td>
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<td>High</td>
<td>LV mass index</td>
<td>0.60**</td>
</tr>
<tr>
<td>Prisant (17)</td>
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<td>RWTd</td>
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</tr>
<tr>
<td>Prisant (17)</td>
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<td>PWTd</td>
<td>0.36**</td>
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<tr>
<td>Verdecchia (18)</td>
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<td>Normal and high</td>
<td>LV mass index</td>
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<tr>
<td></td>
<td></td>
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<td>RWTd</td>
<td>0.36**</td>
</tr>
<tr>
<td>Ravogli (65)</td>
<td>45</td>
<td>Normal</td>
<td>LV mass index</td>
<td>0.38*</td>
</tr>
</tbody>
</table>

Statistical significance: * P < 0.05; ** P < 0.01; *** P < 0.005

BP = blood pressure; IVSd = end-diastolic interventricular septal thickness; LV = left ventricular; LVIDd = end-diastolic LV internal dimension; PWTd = end-diastolic posterior wall thickness; RWTd = end-diastolic relative wall thickness.

N.B.: Prisant (17) found no relation ($r = -0.02$) between single office blood pressures and LV mass index; Verdecchia et al. (18) divided the 24-hour day into periods from 6 a.m. to 6 p.m. and from 6 p.m. to 6 a.m. instead of the periods spent awake or asleep.
Fig. 3. Coefficient of determination \( (r^2) \) of left ventricular mass by systolic blood pressure measured by physicians (open bars) and ambulatory recorder (hatched bars), based on data from Refs. 8-10.

Betwenn 6 p.m. and 6 a.m. than with those between 6 a.m. and 6 p.m. may also be interpreted as supporting this possibility but do not provide conclusive evidence because a significant portion of the waking day was encompassed in their 'nocturnal' 12-hour period.

A more detailed appreciation of the relations between ambulatory blood pressure and LV structure may be obtained from consideration of a study of 100 subjects in our laboratory (10). As may be seen in Table 2, LV mass index was more closely related to systolic than to diastolic blood pressure, similar to findings by other investigators (6, 8, 9, 13). Among all subjects in our study the weak correlation between ventricular mass and casual blood pressure \( (r = 0.24, P < 0.05) \) was only modestly improved by substitution of 24-hour ambulatory systolic pressure \( (r = 0.38, P < 0.001) \), at least in part because of a poor correlation with blood pressures during sleep \( (r = 0.10, P = \text{n.s.}) \). A greater improvement was observed, however, in the 60 subjects in whom systolic blood pressure was measured by portable recorder during occupational work \( (r = 0.50 \text{ versus LV mass index, } P < 0.001) \) (Fig. 4). Parallel findings were observed in the relations between LV mass index and home systolic blood pressures measured by ambulatory recorder, with the closest relation \( (r = 0.48, P < 0.001) \) being found in the 60 subjects who went to work on the day of recording, while the relations between ventricular mass and home pressure did not approach statistical significance either on a non-work day in employed individuals \( (r = -0.02) \) or among non-employed individuals \( (r = 0.07) \).

These findings suggest a special importance with regard to effects on the heart of blood pressure responses to regularly recurring stress at work, with possible 'carry-over' of this effect to blood pressure at home on working days (10, 68). This interpretation is consistent with other evidence that activity and emotional state govern the increases in an individual's blood pressure from relatively basal levels (69).
TABLE 2. Relation between ambulatory diastolic blood pressure and left ventricular structure

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Blood pressure status</th>
<th>Measure of LV structure</th>
<th>Correlation between diastolic blood pressure and LV structure</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Casual BP</td>
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<td>LV mass index</td>
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<td>0.10</td>
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<td>Normal and high</td>
<td>LV mass index</td>
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</tr>
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<td>RWTd</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td>IVSd</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>PWTd</td>
<td>0.20</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LV mass index</td>
<td>0.38**</td>
</tr>
<tr>
<td>White (15)</td>
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<td>High</td>
<td>LV mass index</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PWTd</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gosse (16)</td>
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<td>Normal</td>
<td>LV mass index</td>
<td>0.32**</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PWTd</td>
<td>0.31*</td>
</tr>
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<td>RWTd</td>
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<td>LV mass index</td>
<td>0.37***</td>
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<tr>
<td></td>
<td></td>
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<td>PWTd</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>RWTd</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LV mass index</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Statistical significance: * P < 0.05; ** P < 0.01; *** P < 0.005. Abbreviations: same as Table 1. n.s. = not significant.

N.B.: Prisant (17) found no relation between single office pressures and LV mass index \((r = 0.03)\), PWTd \((r = 0.04)\) or RWTd \((r = 0.04)\). Verdecchia et al. (18) divided the 24-hour day into periods from 6 a.m. to 6 p.m. and from 6 p.m. to 6 a.m. rather than by time awake or asleep.

Alternatively, our data could reflect more accurate sampling of long-term blood pressure levels when a single 24-hour recording is made on a working day, during which activities and stresses are likely to be reasonably representative of those occurring on the approximately 240 working days per year, as opposed to a non-working day, during which activities are likely to be more variable. Further research is needed to elucidate the relative importance of stress responses versus representativeness of blood pressure values in determining the relations between ambulatory blood pressure measurements and LV structure.
Fig. 4. In a study of normotensive and hypertensive adults, left ventricular mass index (vertical axis) was found to be most closely related to systolic blood pressure measured by ambulatory recorder during occupational work (horizontal axis). Reproduced from Devereux et al. (10) by permission of the American Heart Association.

Fig. 5. In a study of normotensive and hypertensive adults left ventricular relative wall thickness (vertical axis) was most closely related to diastolic blood pressure measured by ambulatory monitor during occupational work. Reproduced from Devereux et al. (10) by permission of the American Heart Association.
Diastolic blood pressure

The relation between diastolic blood pressure and cardiac structure has also been explored using ambulatory recorders (Table 2). In general the correlation with LV mass has been less close for diastolic than systolic blood pressure (6, 8–10, 13). However, this has not consistently been the case for indices of LV wall thickness (10, 17). In our series of normotensive and hypertensive subjects (10), the closest correlation ($r = 0.59, P < 0.001$) was in fact that between diastolic blood pressure during occupational work and the ratio of LV wall thickness to chamber radius at end-diastole, termed 'relative wall thickness' (Fig. 5). Since diastolic blood pressure is more closely related to vascular resistance than is systolic pressure, these data extend to the ambulatory setting the evidence of a parallelism that we have reported at rest between the cardiac pattern of concentric hypertrophy and a systemic hemodynamic profile characterized by elevated peripheral resistance (43, 70). This phenomenon may be due to parallel hypertrophy of peripheral resistance vessels and the heart (71–73).

Blood pressure variability

The observation that blood pressure exhibits cyclic variation through the 24-hour day as well as immediate reactivity to a variety of natural and laboratory stimuli (68, 74, 75) has led some investigators to hypothesize that heightened pressure variability might lead to cardiovascular damage in hypertensive patients. Palatini and colleagues (6) found a trend toward more target organ damage — based on a composite score reflecting ECG, chest X-ray and funduscopic abnormalities — in patients with the highest standard deviation of 24-hour systolic or diastolic blood pressures. This result was confirmed by Parati and colleagues (7), who found that the severity of target organ damage — assessed by a similar scoring system — was positively related to the variability of arterial pressure, independently of the average level of ambulatory or casually measured blood pressure. The use of intra-arterial pressure recordings permitted Parati and colleagues (7) to demonstrate that this was true both for short-term variability (the standard deviation of pressure measurements for each 3-second period within each half-hour of the day) and for longer-term variability (the standard deviation of pressure measurements during the 48 half-hour components of the 24-hour period). To date, no data are available concerning the relation of blood pressure variability to LV mass or other direct measures of hypertensive target organ damage.

It is not clear from available data whether exaggerated blood pressure variability is a cause or may represent a consequence of cardiovascular hypertrophy. The latter possibility is supported by a study in which Littler and colleagues (75) found that the standard deviation of intra-arterial blood pressure measurements was inversely related to forearm blood flow reserve after a 4-minute period of venous occlusion. One mechanism by which arterial wall hypertrophy could predispose to enhanced blood pressure variability could be by blunting baroreflex sensitivity, due to the reduction (in accord with the law of La Place) in the stress imparted by a given blood pressure to an artery with a high relative wall thickness. Because blunted post-ischemic vasodilatation is widely accepted as a measure of resistance-vessel hyper-
trophpy (76), these results suggest that vascular hypertrophy may facilitate exaggerated responses to pressor stimuli, thus leading to increased blood pressure variability.

**Relation of ambulatory blood pressure to extracardiac manifestations of hypertension**

Although only limited data are available, it appears that abnormalities in other target organs are also more closely related to ambulatory than to casual blood pressure. Thus, Asmar and colleagues (77) found that systemic arterial stiffness, as estimated by arterial pulse wave-transmission velocity, was closely related to daytime ambulatory systolic blood pressure ($r = 0.69, P < 0.001$), but not to ambulatory diastolic pressure or any aspect of casual blood pressure in 22 patients with sustained essential hypertension. The discrepancy between systolic and diastolic pressure in this study is an expected consequence of fundamental physiological relations, because increased arterial stiffness contributes to elevation of pulse pressure and hence of systolic pressure, but may decrease diastolic blood pressure.

Analogous findings have also been reported with regard to urinary albumin excretion. Giaconi and colleagues (78) observed a significant positive relation ($r = 0.48, P < 0.05$) between average daytime ambulatory diastolic blood pressure — but not casual pressures — and 24-hour urinary albumin excretion in 21 patients with borderline or mild established hypertension. Similarly, Opsahl and colleagues (79) found closer relations between 24-hour systolic blood pressure than office blood pressure for both urinary albumin excretion ($r = 0.44, P < 0.01$ versus $r = 0.31, P < 0.05$) and N-acetyl-$\beta$-d-glucosaminidase excretion ($r = 0.32, P < 0.05$ versus $r = 0.14, \text{n.s.}$). However, Dimmitt and colleagues (80) found microalbumin excretion to be as closely related to clinic as to ambulatory systolic pressures ($r = 0.60$ and 0.52, respectively) in a study of 25 untreated hypertensives in which they also found no relation between retinal abnormalities and any measure of either blood pressure or LV mass.

**III. RELATION OF LEFT VENTRICULAR MASS TO EXERCISE BLOOD PRESSURE**

Athletic conditioning is a well-established stimulus to LV hypertrophy. Because physical exercise causes elevation of arterial pressure as well as heart rate, it has been attractive to speculate that blood pressure during usual physical activity might play a role in determining LV structure in normotensive adults and in patients with hypertension. Unfortunately, interference by muscular activity with non-invasive blood pressure recordings has prevented evaluation of blood pressure during unrestricted physical activity, but valuable information has been derived from studies using exercise testing.

In most studies, systolic blood pressure at the end of maximal (14, 16, 19, 21) or submaximal exercise (20) has been more closely correlated than resting systolic with LV mass ($r = 0.53$ to 0.65, versus $r = 0.16$ to 0.46) (Table 3). Similar results have been obtained using either bicycle ergometry (14, 16) or treadmill exercise by the
TABLE 3. Relation between exercise blood pressure and left ventricular structure

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
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<th>Exercise methodology</th>
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<td>Measure of LV structure</td>
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<td>Treadmill (Bruce)</td>
<td>LV mass</td>
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<tr>
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<td>Treadmill (Bruce)</td>
<td>LV mass</td>
</tr>
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<td>High</td>
<td>Treadmill (Bruce)</td>
<td>LV mass</td>
</tr>
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<td>Normal and high</td>
<td>Bicycle</td>
<td>LV mass</td>
</tr>
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<td>Gosse (16)</td>
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<td>LV mass</td>
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<td>Schmieder (82)</td>
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<td>Bicycle (submaximal)</td>
<td>LV mass</td>
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</tbody>
</table>

Statistical significance: ** P < 0.01; *** P < 0.001.

Bruce protocol (19 – 21), indicating that this finding is independent of the technique employed for exercise testing. Of note, Nathwani and colleagues (20) found that the relation of LV mass to exercise systolic blood pressure was independent of and additive to that with the level of regular physical activity (univariate $r = 0.57$ and 0.44, respectively, yielding a multiple $r$ of 0.68) Similarly, Gottdiener and colleagues (21) found that sedentary men in whom exaggerated blood pressure responses to exercise were associated with high LV mass had no greater maximum oxygen consumption (an objective measure of conditioning) than men with lesser exercise pressure and normal LV mass. This suggests that the relatively close relation between LV mass and blood pressure at peak exercise may reflect the role of cardiac structure as a determinant of the maximum hemodynamic power generated by the heart as much as, or more than, it reflects effects of physical conditioning on ventricular mass and the maximum blood pressure attained during physical exercise (81). Both Gottdiener and colleagues (21) and Schmieder and colleagues (82) found relatively weak relations between LV mass and blood pressure at a fixed level of exercise that was often submaximal.

**Relation of blood pressure to left ventricular function during exercise**

Several investigators have examined the relationship of various measures of blood pressure to LV ejection fraction and pump performance during exercise. In the initial
study, Borer and colleagues (83) found a weak but statistically significant positive relationship between resting systolic blood pressure, based on the mean multiple physician measurements, and radionuclide cine-angiographic LV ejection fraction at rest in 60 unmedicated patients with essential hypertension, whereas the change in ejection fraction from rest to exercise was inversely related to resting systolic pressure. Subsequent studies at Cornell have revealed complex relations among LV functions, LV geometry, and the level of resting blood pressure: essential hypertensive patients with supranormal LV ejection fractions at rest and during exercise had markedly elevated arterial pressure and concentric LV hypertrophy (69) whereas those whose LV ejection fraction at peak exercise was subnormal had more moderate hypertension associated with eccentric LV hypertrophy (84).

Analogous results were reported by Heber and colleagues (85), who found significantly higher resting and daytime intra-arterial blood pressures in 9 hypertensive patients whose radionuclide angiographic LV ejection fraction rose normally with exercise than in 12 with subnormal exercise responses (mean = 183/110 versus 166/97 and 188/124 versus 168/103 mmHg). In another study, Iskandrian and Heo (86) compared LV responses to exercise (assessed by first-pass radionuclide angiography) in 25 normotensive adults with exaggerated systolic blood pressure responses to exercise (> 200 mmHg) with those in 27 normal subjects and in 25 patients with essential hypertension. The subjects with exaggerated exercise blood pressure had the highest exercise cardiac outputs of any group, and had higher LV ejection fractions and lower total peripheral resistances during exercise than the hypertensive patients. Taken together, the studies from Cornell and other centers document a positive relation between LV ejection fraction and blood pressure at rest and during exercise in both normotensive and hypertensive individuals (69, 83 – 86), but suggest that this may depend on the presence of concentric LV hypertrophy, a geometric adaptation associated with an adverse prognosis (53, 58).

IV. RELATION OF AMBULATORY BLOOD PRESSURE TO PROGNOSIS IN HYPERTENSION

To establish the prognostic significance of ambulatory blood pressures it is necessary to follow the same steps as have been accomplished for echocardiographic LV mass, namely to establish partition values that identify abnormal readings with high specificity, to perform longitudinal studies that document the relation between ambulatory pressure level and risk of subsequent complications, and to demonstrate that this predictive value is independent of casual pressure measurements or other conventional risk factors. To date, progress has been made on the first and third of these points, but no data are available concerning the relation between actual ambulatory blood pressure measurements and the risk of complications of hypertension. Although there is not yet a uniformly accepted consensus, information reviewed elsewhere in this volume and other recent studies (111, 112) suggest that the upper limit of normal daytime ambulatory blood pressure falls between 140 and 145/90 mmHg. Night-time and 24-hour pressures exhibit lower normal values but may be less significant with regard to prediction of either target organ changes or complications of hypertension.
Most data concerning the prognostic implications of ambulatory pressure measurements is derived from a large series of patients studied by Perloff and colleagues in San Francisco (22, 24). A total of 1076 patients with at least borderline hypertension based on office blood pressures were studied. The mean age at entry was 45 years, approximately half were women; 314 or 29% of patients underwent ambulatory pressure monitoring on a variety of antihypertensive drugs, and the rest were off medication at the time of assessment. Clinical morbid events had occurred prior to ambulatory monitoring in 225 or 21% of patients, 20% had ECG evidence of LV hypertrophy, one-third had heart enlargement by chest X-ray and one-quarter had at least grade 2 retinopathy. Ambulatory recordings were made at half-hour intervals during 1 or 2 working days by a patient-activated recorder, with 10–40 measurements per patient available for analysis.

During a mean follow-up of approximately 5 years, morbid events occurred in 228

Fig. 6. Estimated cumulative 10-year incidence of first clinical cardiovascular event (fatal or non-fatal) among patients classified according to difference between their observed and predicted ambulatory blood pressure (derived from regression of ambulatory on office blood pressures). RE = regression equation; CV = cardiovascular. Reproduced from Perloff et al. (22) by permission of the American Medical Association.
or 21% of patients, or whom 75 or 7% died. Office and ambulatory blood pressures were both higher, by about 15/5 mmHg, in patients with as opposed to those without new morbid events. The predictive value of ambulatory blood pressure was assessed by dividing patients into those whose ambulatory blood pressure was at least 10 mmHg systolic or 6 mmHg diastolic above ('high') or below ('low') that predicted from office blood pressure, with the remainder falling into an intermediate group. Patients with high ambulatory systolic or diastolic pressures were more likely ($P < 0.002$ to $P < 0.00005$) to experience cardiovascular events or to die during follow-up (Figs. 6 and 7). This difference persisted in subgroup analyses of men and women and of patients who had not suffered cardiovascular events prior to study entry, those with office blood pressure < 160/105 mmHg and those under 50 at the time of ambulatory monitoring, whereas statistical differences were not evident in the smaller subgroups with more severe disease or older age (22). Subse-
quent multivariate analyses of the untreated portion of this population (with mean follow-up of 5½ years) demonstrated that the predictive value of ambulatory blood pressure monitoring was independent of several conventional risk factors and was also present in more severely affected patients (24). Evidence of additional predictive value for subsequent morbid events of ambulatory blood pressure over and above that of office blood pressure was also obtained in a small study by Mann and colleagues (23).

Application of the results of Perloff's large studies (22, 24) to other patients requires that the actual levels of ambulatory blood pressure be estimated. Because ambulatory daytime pressures were substantially lower, by a mean of 16/9 mmHg, than office pressures, a hypothetical patient with the mean office blood pressure of the entire population (161/101 mmHg) who fell into the 'high' group would have daytime ambulatory pressure ≥ 155/98 mmHg whereas one who fell in the low group would have daytime pressure ≤ 135/86 mmHg. Although neither the mean values nor the distribution of office blood pressures in the 'high' or 'low' ambulatory blood pressure group is given, the previous calculation suggests that many (perhaps one-third to half) of those in the 'low' group but only a very small proportion of those in the 'high' group would have what are now considered to be normal daytime ambulatory blood pressures. The results of Perloff and colleagues (22, 24) thus appear to support the inference, based on previous studies of the relations of different measures of blood pressure of LV mass and other target organ changes, that patients with 'white coat hypertension' (elevated office but normal ambulatory pressures) have a benign prognosis. Further analyses of the unique data base of Perloff and colleagues (22, 24), with reporting of actual ambulatory pressures, are eagerly awaited because of their potential to clarify the prognostic significance of both 'white coat hypertension' and differences between office and ambulatory pressures that are both in the elevated range.

V. CLINICAL AND THEORETICAL IMPLICATIONS

Data obtained by ambulatory blood pressure monitoring and echocardiography have altered the understanding of hypertension. The anatomic validation and demonstration of prognostic significance of echocardiographic LV mass makes it a useful 'bioassay' to test the role of different measures of blood pressure in causing cardiovascular disease. Available studies show closer relations between LV mass and blood pressure measured by ambulatory recorder during the daytime or at work than with causal blood pressure (6, 8–18) (Tables 1 and 2). Blood pressure during submaximal or maximal exercise is also more closely related than casual pressure to LV mass (Table 3). Finally, the studies of Perloff and colleagues (22, 24) suggest, despite the indirect method of analysis, that ambulatory pressure measurements may also be superior for predicting the prognosis of hypertension. Taken together, these studies reveal a closer parallelism between LV structure (and probably clinical risk) and blood pressure during mental and physical activity than with clinical measurements of blood pressure.

These results have important implications for the diagnosis and classification of severity of hypertension. Although physician and ambulatory blood pressure recor-
readings are highly correlated, discordances are common. Daytime or workplace ambulatory pressures are lower than clinic pressures in most but higher in some hypertensive patients (7, 87–89), whereas the reverse is commonly true among normotensives (89). As many as 20% of adults currently diagnosed as hypertensive are normotensive outside of the doctor’s office, thus exhibiting ‘white coat hypertension’ (90). As expected from previous results, patients with ‘office hypertension’ but normal ambulatory blood pressures appear to have normal LV structure and function (91). Thus, many patients currently classified as hypertensive may instead have benign hyperreactivity of blood pressure to physician measurement.

Based on evidence that echocardiographic LV hypertrophy (51–60) and elevated ambulatory blood pressure (22–24) both predict an adverse prognosis, whereas normal ambulatory pressure identifies a relatively benign prognosis, it appears possible to stratify patients with office hypertension into groups at high, low and intermediate risk on the basis of these two tests (Fig. 8). In addition, many treated hypertensive patients may have ambulatory pressures in the normal range but elevated office pressures that would lead to more intensive antihypertensive therapy (92). Although the concept of a J-shaped relation between the degree of blood pressure reduction induced by treatment and coronary disease risk remains controversial, it is possible that excessive pressure-lowering may contribute to the disappointing results of conventional antihypertensive treatment (93, 94). Further research is needed to verify the prevalence of ‘white coat hypertension’ and overtreatment of hypertension and to determine whether patient outcome is improved by use of ambulatory pressure recordings or echocardiographic LV mass measurements to guide antihypertensive treatment.

The observed pattern of relations between different measures of blood pressure and cardiac structure also has potentially important theoretical implications. The

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**Fig. 8.** Hypothesized relation, based on presently available data, of the risk of cardiovascular complications to left ventricular mass and ambulatory blood pressure in hypertensive patients.
closer relations between LV mass and arterial pressure during mental or physical activity suggest a mechanism whereby stresses of various types might exert adverse cardiovascular effects. In fact, we have recently observed a significant relation, in a population of employed men, between job 'strain' (high job demands and low decision-making latitude) and ambulatory blood pressure as well as LV mass (95). Under this interpretation one would postulate the following chain of adverse events: stress → elevated blood pressure → cardiovascular hypertrophy → clinical morbid events. This hypothesis, which needs further verification, provides a possible explanation for epidemiological relations between job characteristics and cardiovascular morbidity (96, 97).

However, the converse explanation of the observed phenomena is also possible: LV hypertrophy might be closely related to blood pressure during stress or activity because increased LV mass provides the circulation with a pump that generates more hemodynamic power in response to the neural and humoral systems that regulate blood pressure (98). Under this hypothesis, a larger LV mass due to genetic, neurohumoral or other factors could actually participate in the mechanism of blood pressure elevation. Preliminary support for this view has been provided by the report by Mahoney and colleagues (99) that baseline LV mass in children and adolescents contributed independently to prediction of subsequent blood pressure, in addition to the information provided by baseline rest and exercise blood pressures. Similarly, in a study of 132 initially normotensive adults we found that LV mass measured at baseline examination and the ratio of dietary sodium to potassium intake were the only variables that predicted the development of mild hypertension during 5 years of subsequent follow-up (100). Additional research is needed to evaluate the mechanism of these observations.

One further implication of the available data deserves comment. No matter what component of blood pressure is used, or in what setting, the relation between blood pressure and LV mass appears to reach a ceiling at correlation coefficients of about 0.65 in highly selected series and of about 0.50 in more representative populations (Tables 1–3). While this phenomenon has been interpreted as support for the hypothesis that non-hemodynamic factors are important regulators of LV mass in

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Multiple regression equation:
$$LVMI = 2.2 + 0.87SBP + 0.69 \text{ stroke index} - 17.4 \text{ ESS/ESVi}; r = 0.81; P < 0.00001$$

ESS = end-systolic meridional wall stress; ESVi = end-systolic volume index; LV = left ventricular; LVMI = LV mass index; SBP = systolic blood pressure. Adapted from data of Ganau et al. (103).
Fig. 9. Three-dimensional plot of the interrelations revealed by multivariate analysis among left ventricular (LV) mass index, systolic blood pressure, stroke index, and LV contractile performance (ESS/ESVi ratio). The two planes depicted correspond to different levels of LV mass index (75 and 110 g/m², respectively). Each plane describes the possible interactions between systolic pressure, stroke index, and ESS/ESVi responsible for a given level of LV mass index. Displacements between planes due to changes in blood pressure (A–B), contractility (C–D), or stroke volume (C–E) are indicated. Reproduced from Ganau et al. (103) by permission of the American Heart Association.

hypertension (101, 102), recent research from our laboratory suggests that it may be explained by hemodynamic factors. Thus, in a study of 100 normotensive or mildly hypertensive adults (103), we found that echocardiographic LV mass exhibited relations, of approximately equal strength, directly with standardized technician measurements of systolic blood pressure and LV stroke volume (a measure of hemodynamic volume load), and inversely with the LV end-systolic stress/end-systolic volume index ratio, an indirect index of LV contractility (Table 4). These relations were all statistically independent of each other ($P < 0.0001$), and when considered together revealed a three-dimensional model of the determinants of LV muscle mass (103) (Fig. 9).

Experimental support for the three-dimensional model of stimuli to LV hypertrophy comes from a study in which we used high-resolution echocardiography (104) to reveal greater LV mass in rats with one-kidney, one-clip Goldblatt hypertension — a model in which volume overload coexists with pressure overload — than in two-kidney, one-clip rats with equal blood pressure elevation (105). Other investigators have shown that increased blood pressure without a change in contractility or LV
stroke volume led to a proportionate increase in LV mass (106) whereas inotropic stimulation blunted the hypertrophy response to pressure overload (107). Conversely, blood pressure reduction with vasodilators did not cause the expected decrease in LV mass because of offsetting LV volume overload (108 – 110). Taken together, these results suggest that refinement of methods of blood pressure measurement may not be able to improve further the relations between pressure level and LV mass, and that the predictive value of LV mass and ambulatory blood pressure for complications of hypertension are likely to be at least partially independent of each other and additive.

ACKNOWLEDGEMENTS

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15. Analysis of blood pressure data

Douglas G. Altman and J. Martin Bland

In this chapter we consider several aspects of the statistical analysis of blood pressure measurements.

First we look at sources of variation in blood pressure measurements. We then describe the distribution of blood pressure as a variable for use in statistical analysis. We look at the distribution of blood pressure from subject to subject and also at the distribution of repeated measurements of blood pressure for the same subject.

We then look at the design and analysis of studies for the evaluation of blood-pressure-measuring devices, and consider both the repeatability of measurements using a particular device and the agreement between two different devices.

We then consider problems arising from regression towards the mean, a statistical phenomenon of particular importance in the study of hypertension. We describe situations in which this might occur, the magnitude of possible effects, and a technique for their estimation. Lastly, we look at the relationship between the initial blood pressure level and the differences between this and subsequent measurements.

We shall illustrate some of these points using a set of data in which 2 observers made 3 pairs of simultaneous readings on each of 85 subjects using a sphygmomanometer. The data are shown in Table 1.

1. SOURCES OF VARIATION IN BLOOD PRESSURE MEASUREMENT

In this section we consider the sources of measurement error in blood pressure measurement. By ‘error’ we mean the variation in measurements which occurs due to the lack of precision in instruments, the limitations of reading numbers from scales, the natural variability of blood pressure from heartbeat to heartbeat and so on. We do not mean mistakes.

When we measure blood pressure, the number we obtain is one of many possible measurements on that subject. Table 2 shows 3 pairs of simultaneous measurements made by 2 observers on the same subject. These data suggest that there is variation in measured pressure between observers when measuring the same instantaneous pressure, and also between pairs of measurements, i.e. from measurement to
TABLE 1. *Blood pressure data for 85 subjects numbered 1 – 85, by simultaneous observers A and B, each making 3 observations of systolic and diastolic pressure*

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TABLE 1. (continued)
measurement. Here time and observer are different sources of variation. Ideally we would like to have simultaneous measurements by the same observer, but this is impossible.

Table 1 shows repeated measurements made by trained observers for 85 subjects. We now have a third source of variation, between subjects. We can separate the variability that we get from observer to observer and from time to time, to see what effect these different sources of variability have. We can present this in the form of standard deviations. The standard deviation of repeated measurements made simultaneously in the same subject is 3.4 mmHg diastolic, 3.3 mmHg systolic. This ignores any systematic differences between observers and just treats them as repeated observations.

The standard deviation can be estimated for each subject individually to see how it varies across the range of pressure. As Figure 1 shows, when we plot the standard deviation of simultaneous measurements against the mean for that subject, we see no evidence of any relationship between standard deviation and mean.

The standard deviation between measurements at different times on the same subject is 5.5 mmHg diastolic, 5.5 mmHg systolic. This is greater than for simultaneous measurements and reflects the natural variability of blood pressure from measurement to measurement. It suggests that it is pressure which is itself varying which produces much of the ‘measurement’ error. This standard deviation, too, is unrelated to the mean (Fig. 2). Blood pressure is a rather variable quantity. The variation above is short-term, being over a few minutes. There may be greater variations than this over longer periods, hours or days.

The third source of variation in Table 2 is of course that between subjects. These subjects were not a random or representative sample of any population, but were chosen to give a wide range of pressures. As the data were collected to investigate an automated sphygmanometer, it was important to consider a wide range.

The variability between repeated measurements is of the same order of magnitude as some of the changes we hope to bring about in blood pressure management. This may lead to apparent labile hypertension. A patient whose average pressure is around the cut-off point for a diagnosis of hypertension may by chance have a measurement above the cut-off or one below just by chance.

We may get a better estimate of the individual’s pressure by taking several measurements and averaging them. We can calculate the gain in precision which this brings. The standard error of the mean of several measurements is given by the usual formula, \( s / \sqrt{n} \), where \( s \) is the standard deviation. We expect that about 95% of means of \( n \) blood pressure measurements will lie within two standard errors of the subject’s mean of all possible measurements, i.e. their ‘true’ or ‘mean’ blood pressure.

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**TABLE 2.** Three pairs of simultaneous measurements of systolic pressure by two observers on the same subject, drawn from Table 1
Fig. 1. Standard deviation against subject mean for simultaneous measurements on the same subject.

Fig. 2. Standard deviation against subject mean for repeated measurements on the same subject.

pressure. Table 3 shows the effect of taking different numbers of measurements of systolic and diastolic blood pressure.

II. THE DISTRIBUTION OF BLOOD PRESSURE

Many techniques of statistical analysis, such as regression analysis, require that the variable being analyzed follows a Normal Distribution. In this section we investigate the distribution of blood pressure measurements, both for blood pressure itself and for measurement errors in blood pressure. As blood pressure is often said to follow a Log Normal Distribution, we investigate the effects of logarithmic transformation on both blood pressure and measurement error.

The distribution of repeated measurements for a single subject

The variations in measured pressure within the same subject over a short time appear to follow a Normal Distribution. To demonstrate this we would ideally like large numbers of measurements on each of a number of subjects spanning the range of blood pressure. We can use the data of Table 1, however, if we calculate devia-
TABLE 3. Effect on variability of using the mean of more than one blood pressure measurement

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The distribution of blood pressure within the subject for the data of Table 1, together the Normal Distribution with the same mean and standard deviation. Figure 3 was constructed by taking each group of 6 measurements for the subject and subtracting the subject's mean from each of the observations. The resulting differences enable us to examine the variability of blood pressure measurements within the subject. As Figure 3 shows, the distribution is very close to the Normal.

The distribution of blood pressure in the general population

The distribution of blood pressure between subjects does not show the same adherence to the Normal Distribution as does that within subjects. Figure 4 shows the distribution of diastolic blood pressure in a Scottish population (1). For both men and women, the raw data are noticeably skew to the right. A logarithmic transformation has the effect of removing this skewness. When the distribution is

![Figure 3](image-url)

*Fig. 3. Distribution of repeated blood pressure measurements on the same subject (differences from the subject mean).*
Fig. 4. Distribution of diastolic pressure and corresponding Normal Distribution for 3000 Scottish adults. From Hawthorne et al. (1).

Fig. 5. Systolic blood pressure in 3 populations. From Rose (3).

shown on a logarithmic scale, the Normal Distribution appears to fit the log-transformed data well (Fig. 4). This pattern is seen in other data sets, e.g. in the U.K. Regional Heart Study (2). However, there are no theoretical grounds known to us for expecting blood pressure to follow a Log Normal Distribution, and the log transformation must be regarded as empirical. It does not always work. Figure 5 shows the distribution of systolic blood pressure in 3 different communities (3): African nomads, English civil servants and Japanese railway workers. Rose (3) comments that ‘when mean pressures are low, the distribution is approximately Normal, but with increasing mean there is a flattening (kurtosis) and positive skewing.’ Figure 5 also shows the 3 distributions plotted on a logarithmic scale. Some skewness is still apparent in the London and the Japanese data.
The implication of this is that when analyzing blood pressure, e.g. by multiple regression analysis, log-transformed pressures may be preferable to the raw data. The departure from the Normal Distribution in Figure 4 is not very great, however, and for some purposes it will not make much difference whether raw or transformed data are used, particularly if samples are large.

**Implications of log-transformation on measurement error and studies of change**

If we log-transform blood pressure data for analysis, this might affect the approximate Normal Distribution of measurement errors, and lead to difficulties. Figure 6 shows the distribution of differences of log-transformed pressure about the subject mean. As the figure shows, the distribution remains Normal. The log-transformation has no effect on the measurement error. This is because the process of subtraction itself tends to make differences follow a Normal Distribution (4). Also, blood pressures are sufficiently far from zero for the log transformation to have only a small effect on the distribution. Thus the distribution of differences within the subject is approximately Normal whether the pressure is log-transformed or not.

![Figure 6: Distribution of repeated logarithmically transformed blood pressure measurements on the same subject (differences from the subject mean).](image1)

![Figure 7: Distribution of the change in diastolic pressure over 1 year and corresponding Normal Distribution for 3000 Scottish adults. From Hawthorne et al (1).](image2)
Figure 7 shows the changes in diastolic pressure over 1 year in the data of Hawthorne and colleagues (1). The changes show a distribution very similar to the Normal. Although we cannot calculate the differences for log-transformed pressures in this study, we would expect those too be Normal.

The distribution of blood pressure in hypertensive patients

The distribution of blood pressure in hypertensive patients is the right tail of the distribution for the population as a whole. Because of this, the distribution tends to be highly skew when these subjects are remeasured. Figure 8 shows systolic pressure at 28 weeks' gestation for a sample of pregnant women, selected as having diastolic $\geq 85$ or systolic $\geq 140$ mmHg at booking (St. George's Birthweight Study) (5). [This selection rule was chosen to get sufficient women to display the distribution and does not imply that these women were hypertensive. The higher the cut-off chosen, the greater will be the skewness in the resulting distributions of blood pressure]. As Figure 8 shows, the distribution remains skew on the logarithmic scale. The departure from the Normal Distribution is considerable and may well have an effect on analytical methods, such as t-tests and regression, which rely on an assumption that data are Normally distributed.

We can find an empirical transformation which gives a reasonable approximation to the Normal Distribution by subtracting a constant before log-transforming. Figure 8 also shows the effect of subtracting 80 mmHg. The shape of the distribution on the natural scale is unchanged, but the log-scale gives a much more symmetrical shape. This type of transformation will usually work reasonable well. The

![Graphs showing distribution of blood pressure](image)

Fig. 8. Distribution of systolic pressure at 28 weeks' gestation in a group of 56 pregnant women chosen because booking pressure was high.
constant to be subtracted will depend on the data and can be found by trial and error.

The advantage of a Normalizing transformation, resulting in more valid tests of significance and increased power, must be set against the disadvantage of the difficulty in relating estimates to the original scale. This problem does not occur if we analyze changes in blood pressure, and in the case of hypertensive subjects this is often of more interest than absolute pressure levels.

III. COMPARING BLOOD-PRESSURE-MEASURING DEVICES

A vast number of devices have been developed for measuring blood pressure. As a consequence, a huge number of papers have been published in which two or more methods have been compared. Unfortunately, many of these comparisons have been based upon inappropriate statistical analysis. We will first describe some simple valid approaches to the problem. We will then describe methods for assessing and comparing the reproducibility of different devices. Lastly, we will explain why some common approaches to method comparison are invalid.

Asking the right question

The questions to be asked in method comparison studies fall into two categories:

(a) Properties of each method
   How repeatable are the measurements?

(b) Comparison of methods
   Do the methods measure the same thing on average? That is, is there any relative bias? What additional variability is there? This may include both errors due to repeatability and errors due to patient–method interactions. We summarize all this as 'error'. These quantities are often called 'accuracy' and 'precision' respectively.

[Under properties of each method we could also include questions about variability between observers, between times, between places, between position of subject, etc.]

We emphasize that this is a question of estimation, both of scatter and bias. What we need is a design and analysis which provide estimates of both scatter and bias. No single statistic can estimate both.

It is difficult to produce a method that will be appropriate for all circumstances. We feel that a relatively simple pragmatic approach is preferable to more complex analyses. What follows is a brief description of the basic strategy that we favor; clearly the various possible complexities which could arise might require a modified approach, involving additional or even alternative analyses.

The analysis will be illustrated using the data in Table 4, which shows two diastolic blood pressures made by observer A (readings 2 and 3 from Table 1) and two simultaneous readings made by a machine (M).
TABLE 4. Diastolic blood pressure recorded by observer A using a sphygmomanometer and simultaneously by an automated blood-pressure-measuring device (M)

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Difference 1 is the difference (A - M) for the first reading, and Difference 2 the average difference for the two readings.
Comparison of methods

The main emphasis in method comparison studies clearly rests on a direct comparison of the results obtained by the alternative methods. The question to be answered is whether the methods are comparable to the extent that one might replace the other with sufficient accuracy for the intended purpose of measurement.

The obvious first step, one which should be mandatory, is to plot the data. We first consider the unreplicated case, comparing methods A and M. Figure 9 compares a single reading of diastolic blood pressure by methods A and M. Plots of this type are very common and often have a regression line drawn through the data. The appropriateness of regression will be considered in more detail later, but whatever the merits of this approach the data will always cluster around a regression line by definition, whatever the agreement. For purposes of comparing the methods the line of identity (A = M) is much more informative, and is essential to get a correct visual assessment of the relationship. Although this type of plot is very familiar and in frequent use, it is not the best way of looking at this type of data, mainly because much of the plot will often be empty space. Also, the greater the range of measurements, the better the agreement will appear to be. Thus, if diastolic and systolic pressures are shown in the same graph, the agreement will appear better than if two graphs are used.

It is preferable to plot the difference between the methods (A - M) against (A + M)/2, the average. This plot shows explicitly the differences in blood pressure, and also indicates whether the distribution of the differences varies according to the level of blood pressure. Figure 10 shows the data from Figure 9 replotted in this way. From this type of plot it is much easier to assess the magnitude of disagreement (both error and bias), spot outliers, and see whether there is any trend, e.g. an increase in A - M for high values. This way of plotting the data is a very powerful way of displaying the results of a method comparison study. It is closely related to the usual plot of residuals after model-fitting, and the patterns observed may be similarly varied.

![Graph](image)

*Fig. 9. Relation between single diastolic blood pressure recordings by observer A and machine (M).*
The quantification of agreement is based on both the average difference between the methods of measurement and the variability in the differences. The average agreement between the two sets of blood pressure measurements is the mean of the differences from each subject (and is equal to the difference between the overall means). There are 3 approaches to the assessment of the variability component of agreement:

(a) We can calculate the proportion of differences that are more than some reference value, say 10 mmHg. The reference values can be superimposed on the scatter diagram.

(b) We can calculate directly the values outside which a certain proportion, say 10%, of the observations fell. We do this simply by ordering the data and taking the range of values left after removing a percentage of the sample from each end. These values can also be superimposed on the scatter diagram.

(c) We can calculate the standard deviation of the within-subject differences. Using the assumption that the differences will have a Normal Distribution, which is usually reasonable for blood pressure data, we can calculate the range of values which we expect would encompass the large majority of within-subject differences. We call these two values the ‘limits of agreement’ (6). For example, we expect 95% of differences to lie between mean $-1.96$ SD and mean $+1.96$ SD. These values can also be superimposed on the scatter diagram. The value of 1.96 is often rounded to 2.

Methods (a) and (b) do not require any assumptions about the distribution of the differences, but they are generally less reliable than those obtained using Normal Distribution theory, especially in small samples. If there are one or more outliers (extreme discrepancies between methods), however, an empirical approach may be preferable. Method (a) is illustrated in O’Brien and colleagues (7) using data from the same data set. Here we will use method (c).

Figure 11 shows the 95% limits of agreement ($-14.9$ to $13.0$ mmHg) superimposed on the data from Figure 10. We think that this type of figure gives a splendid summary of the comparison of the two methods.
Fig. 11. 95% limits of agreement superimposed on Fig. 10.

Properties of each method: repeatability

The assessment of repeatability is an important aspect of studying alternative methods of measurement. Replicated measurements are, of course, essential for an assessment of repeatability, but to judge from the medical literature the collection of replicated data is rare.

Repeatability is assessed for each measurement method separately from replicated measurements on a sample of subjects. We obtain a measure of repeatability from the within-subject standard deviation of the replicates.

It is important to ensure that the within-subject repeatability is not associated with the size of the measurements, in which case the results of subsequent analyses might be misleading. The best way to look for an association between these two quantities is to plot the standard deviation against the mean. If there are two replicates $x_1$ and $x_2$, then this reduces to a plot of $\mid x_1 - x_2 \mid$ against $(x_1 + x_2)/2$. From this plot it is easy to see if there is any tendency for the amount of variation to change with the magnitude of the measurements. The (rank) correlation coefficient can be tested against the null hypothesis of $r = 0$ for a formal test of independence.

Figures 12 and 13 show these plots for the data in Table 5. Neither shows any tendency for the variability to change with the level of blood pressure and the rank correlation coefficients between the absolute difference and mean are $-0.06$ and $-0.01$ respectively.

If the within-subject repeatability is found to be independent of the size of the measurements, then a one-way analysis of variance can be performed. The residual standard deviation is an overall measure of repeatability, pooled across subjects. With two replicates the residual SD can be obtained simply from the between-replicate differences ($d_i$) as (4):

$$s_{res} = \sqrt{\frac{\Sigma d_i^2}{n}}$$
We can say that the difference between two replicate measurements would be within $2.83 \sigma_{res}$ on 95% of occasions (8).

For our blood pressure data the residual SD for the human observer (A) and machine (M) are 5.57 and 5.19 mmHg, so that differences greater than 15.8 and 14.7 mmHg, respectively, are unlikely.

If, however, an association between differences and means is observed, the results of an analysis of variance could be misleading. Several approaches are possible, the simplest of which is to define the repeatability as a function of the size of the measurement. This problem does not usually arise with blood pressure data, except that sometimes there are a few large discrepancies for subjects with very high blood pressure.
Properties of each method: other considerations

Many factors may affect a measurement, such as observer, time of day, position of subject, particular instrument used, laboratory, etc. The British Standards Institution (9) differentiates between repeatability, described above, and reproducibility, 'the value below which two single test results . . . obtained under different conditions . . . may be expected to lie with a specified probability'.

In general when comparing blood-pressure-measuring devices, the interest is in repeatability rather than reproducibility. We know that blood pressure varies markedly throughout the day, for example. One area of interest is the comparison of observers. If the aim is to estimate variability among a representative group of observers, then the observations can be treated as replicates, as already described. If, however, specific observers are compared, e.g. when comparing an inexperienced observer and an experienced observer, the approach used to compare different methods, described below, should be used.

Multiple measurements

In order to assess the repeatability of methods of measuring blood pressure we need at least two measurements per subject with each method (i.e. two or more simultaneous readings using each device). We certainly recommend that multiple measurements are taken, as the assessment of repeatability is an important component of comparing devices. There are important implications for the assessment of agreement, however.

Firstly, it is possible to treat the repeated measurements on each subject as independent. This approach is reasonable if the pairs of readings with each device are simultaneous, but is not acceptable otherwise. A safer general approach is to analyze each subject's mean blood pressure using each device. It is essential, however, to make an adjustment to the results to allow for the fact that this averaging was performed. Bland and Altman (6) give details. If the adjustment is not made, there will be a falsely optimistic assessment of between-device agreement. For example, the 95% limits of agreement for the comparison of A and M using the mean of the two replicates in Table 5 are $-12.4$ to $10.9$ mmHg, some 16% narrower than the values based on one replicate.

Incorrect methods of analysis

None of the approaches discussed below adequately tells us whether the two methods agree adequately. We think that the common use of these methods indicates a failure to consider the true purpose of the comparison.

Correlation

By far the most common approach to method comparison is to calculate the product–moment correlation coefficient ($r$) between the two methods of measurement. The correlation coefficient depends on both the variation between individuals (i.e. between the true values) and the variation within individuals (measurement er-
error). The observed correlation coefficient will thus partly depend on the choice of subjects. If the variation between individuals is high compared to the measurement error, the correlation will be high, whereas if the variation between individuals is low, the correlation will be low.

Diastolic blood pressure varies less between individuals than does systolic pressure, so we would expect to observe a worse correlation for diastolic pressures when methods are compared in this way. For example, Hunyor and colleagues (10) presented 7 pairs of correlation coefficients, for which this phenomenon was observed every time (Table 5). This is not an indication that the methods agree less well for diastolic than for systolic measurements.

The correlation coefficient is not a measure of agreement; it is a measure of association. It is quite wrong to infer from a high correlation that two methods agree well or may be used interchangeably:

(a) $r$ measures the strength of a relation between two variables, not the agreement between them. We will have perfect agreement only if the points in a scatter diagram lie along the line of equality, but we will have perfect correlation if the points lie along any straight line.
(b) Correlation depends on the range of the true quantity in the sample. If this is wide, the correlation will be greater than if it is narrow. Since investigators usually try to compare two methods over the whole range of values typically encountered, a high correlation is almost guaranteed.
(c) The test of significance may show that the two methods are related, but it would be amazing if two methods designed to measure the same quantity were not related. The test of significance is irrelevant to the question of agreement.
(d) Data which seem to be in poor agreement can produce quite high correlations.

**Regression**

Linear regression is another misused technique in method comparison studies. Often the slope of the least-squares regression line is tested against zero. This is equivalent

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Between subject standard deviations are $s_A$ and $s_B$. From Hunyor et al. (10).
to testing the correlation coefficient against zero, and the above remarks apply.

A more common approach is to compare the slope of the regression line against 1. The implied argument is that if the methods are equivalent the slope of the regression line would be 1. However, this ignores the fact that both dependent and independent variables are measured with error, resulting in the expected slope being less than 1. How much less than 1 depends on the amount of measurement error of the method chosen as 'independent'. Similarly, the expected value of the intercept will be greater than zero because of the bias in the slope. Thus the conclusion of Ross and colleagues (11) that 'with a slope not differing significantly from unity but a statistically highly significant y-intercept, the presence of a systematic difference . . . is demonstrated' is unjustified. Likewise, it is incorrect to interpret the intercept as the systematic bias between the methods of measurement, e.g. Sloan et al. (12).

We also note that the residual standard deviation from the regression analysis is a measure of the scatter of points around the regression line, and will always be less than the standard deviation of the between-method differences, which is the scatter of the points around the line of equality.

More complex forms of regression, which allow for error in both variables, can be used. However, these are complex to apply and not that easy to interpret. A simpler solution is thus preferable.

Comparing means

The values obtained by the two methods can be compared by the paired $t$-test (or the paired Wilcoxon test). In the $t$-test the mean difference between the methods is related to its standard error (SE). The SE is derived from the standard deviation of the within-subject differences between methods. Clearly, therefore, the greater the variability of these differences, the less likely is it that the mean difference will be significantly different from zero. This method thus gives the opposite of what is required — the worse the agreement, the more likely we would be to have a non-significant difference, and hence conclude that agreement is acceptable. Further, if there is no difference on average between two methods, the test will yield a non-significant answer regardless of the degree of agreement (indeed, even if the values from the two devices are uncorrelated).

Analysis of variance

Two-way analysis of variance can be used to compare methods of measuring blood pressure. This approach may be especially attractive when the subjects are measured more than once. However, the method is inherently unsuitable because it includes the assumption that the two methods are equally repeatable, which is one of the things that we wish to assess. [In contrast, it is perfectly reasonable to use one-way analysis of variance to get an estimate of repeatability from data comprising multiple measurements using one device.]
IV. REGRESSION TOWARDS THE MEAN

Use of the term 'regression'

'Regression' comes from a Latin root meaning 'going back'. In statistics, it means something quite different, and refers to the procedures for fitting expressions such as \( y = a + bx \). The origin of this was a paper by Francis Galton (13), 'Regression towards Mediocrity in Hereditary Stature'. Galton collected the heights of parents and of their adult children. He related the heights of the children to the average height of their parents, which he called the 'midparent'. He also made an adjustment for sex, multiplying female heights by 1.08, but this is not important here. Figure 14 is adapted from his paper. Note that the mean height is the same for child and parent, 68.2 inches. The ranges are not, because the midparent is an average of two observations and thus has its range reduced by a factor of about \( 1/\sqrt{2} \). Now, consider those parents with midheight between 70 and 71 inches. Their children have a range of heights between 66 and 73 inches, and a mean height of 69.5 inches. The mean height of the subgroup of children is closer to the mean height of all children than is the mean height of the subgroup of midparents to the mean height of parents. This phenomenon Galton called 'regression towards mediocrity', what we now call 'regression towards the mean'. Note that the same thing happens if we start with the children. Consider the children with height between 70 and 71 inches. The mean height of their midparents is 69.0 inches. This is a statistical, not a genetic, phenomenon.

Now, if we take each group of midparents by height and calculate the mean height of their children, these means will lie on a straight line. This line came to be called the 'regression line', and hence the process of fitting such lines became known as 'regression'. In Galton's terminology, there was no regression if the points lay exactly on a straight line. In modern terminology, there is said to be 'no regression' if there is no relationship between the variables at all. Hence, the modern usage is directly converse to the original meaning. We use the term 'regression towards the

![Figure 14](image-url) Galton's original data showing the relationship between the heights of children and their parents (13). The size of each circle is proportional to the number of coincident points.
mean' to describe Galton's regression, and say there is no regression towards the mean to describe his case of no regression [The use of the symbol ‘r’ for the correlation coefficient is another relic from this confusion of terms.]

Regression towards the mean in blood pressure studies

Suppose we select subjects with high pressure, e.g. diastolic blood pressure over 95 mmHg. We then treat these and re-measure them at a later date. The mean blood pressure has gone down. However, if we do nothing at all, the mean blood pressure goes down, too, due to regression towards the mean. The first measurement and the second are related, and have the same mean and variance. However, not all patients with diastolic pressure over 95 mmHg will have this on the second occasion, due to random variation, and the mean for the high blood pressure group is reduced. Figure 15 illustrates the phenomenon using two measurements from 4 subjects. Cases A and B have diastolic greater than 95 mmHg on the first occasion, and so are included in the treatment group and measured again. Case A has diastolic below 95 mmHg on the second occasion, case B does not change, and so the mean for the included group on the second occasion is lower than on the first. Case C, on the other hand, was lower than 95 mmHg on the first occasion and higher on the second, but was not included and so the second measurement would not be taken. The mean and standard deviation for all subjects would be the same on the first and second occasions, but the selection effect produces a decrease in the mean for the included, high-pressure group and an increase for the excluded, low-pressure group.

It is worth stressing that regression towards the mean is a purely statistical phenomenon, related to the way data are collected and our inability to measure without error, not a biological phenomenon. If repeated blood pressure measurements on the same subject were always identical, regression to the mean would not occur.

Regression towards the mean and the correlation coefficient

Firstly we follow Healy and Goldstein (14) and define variables \( x \) and \( y \), with means

![Graph](image)

*Fig. 15. How selection of subjects with high pressure produces regression towards the mean.*
\( \mu_x \) and \( \mu_y \), standard deviations \( \sigma_x \) and \( \sigma_y \), and correlation \( \rho \). The expected coefficients of the least squares regression equation can be written:

\[
y = \mu_y + \rho \frac{\sigma_y}{\sigma_x} (x - \mu_x)
\]

where \( \rho \sigma_y / \sigma_x \) is the expected value of the regression coefficient. This is not our usual formation of a regression equation, but it is consistent with the usual \( y = a + bx \) (see Appendix). Thus a change of one standard deviation in \( x \) is associated with a change of \( \rho \) standard deviations in \( y \). Now unless \( x \) and \( y \) are always equal, \( \rho \) is less than one. This means that for a given value of \( x \), the predicted value of \( y \) is always fewer standard deviations from its mean than \( x \) is from its mean. Regression towards the mean always occurs unless \( \rho = 1 \), perfect correlation.

**Calculation of the expected regression towards the mean**

In the special case of regression towards the mean in blood pressure, we can find a simple estimate of the regression effect (15). This solution applies only to the particular case of selecting subjects with high initial measurements and measuring them again later. More general solutions to regression towards the mean problems are given by Davis (16) and James (17).

We observe a blood pressure measurement (\( x \)) on a group of subjects drawn from the general population. These have a mean \( \bar{x}_{\text{pop}} \), the mean of a sample of the whole population, hypertensive or not. We then choose all those with blood pressure above some value, whom we label as hypertensive. The mean for these is \( \bar{x}_{\text{hyp}} \), the mean of the hypertensive sample. If we did nothing at all to these subjects, but simply called the hypertensive group back and measured them again to give measurement \( y \) with mean \( \bar{y}_{\text{hyp}} \), then we expect that \( \bar{y}_{\text{hyp}} \) will be less than \( \bar{x}_{\text{hyp}} \) because of the regression towards the mean effect.

The observed mean \( \bar{y}_{\text{hyp}} \) will be less than the value we might expect (\( \bar{x}_{\text{hyp}} \)) by an amount which we obtain from the general regression towards the mean equation. We can solve this easily for this particular case. The standard deviations \( \sigma_x \) and \( \sigma_y \) are equal, because both are the standard deviation of blood pressure in the general population. They therefore cancel out in the expression \( \rho \sigma_y / \sigma_x \). \( \rho \) is the correlation between the successive measurements \( x \) and \( y \) in the whole population. We can estimate both \( \mu_x \) and \( \mu_y \), which are each the mean blood pressure in the general population, by \( \bar{x}_{\text{pop}} \). The expected value of the second measurement for an individual (\( y \)), given the value of first measurement for that individual (\( x \)), is estimated by:

\[
\bar{x}_{\text{pop}} + \rho (x - \bar{x}_{\text{pop}})
\]

We find the expected value of the mean for the second measurement in the selected, hypertensive group (\( \bar{y}_{\text{hyp}} \)) by averaging the regression to the mean equation over
members of the hypertensive sample to give:

\[ \bar{x}_{\text{pop}} + \varrho(\bar{x}_{\text{hyp}} - \bar{x}_{\text{pop}}) \]

The difference between \( \bar{x}_{\text{hyp}} \) and \( \bar{y}_{\text{hyp}} \) is the regression towards the mean effect, the amount by which we estimate that the mean of the hypertensive group will fall if nothing happens to their blood pressure other than the random variation which produces measurement error. Subtracting the expected value of \( \bar{y}_{\text{hyp}} \) from \( \bar{x}_{\text{hyp}} \) we get:

\[ \bar{x}_{\text{hyp}} - [\bar{x}_{\text{pop}} + \varrho(\bar{x}_{\text{hyp}} - \bar{x}_{\text{pop}})] \]

\[ = (1 - \varrho)(\bar{x}_{\text{hyp}} - \bar{x}_{\text{pop}}). \]

This is the fall in mean pressure that we would expect in our hypertensive sample due to regression towards the mean, i.e. due to the measurement and selection process alone. We can see from this that the greater the mean for the hypertensive sample (\( \bar{x}_{\text{hyp}} \)), the greater is the expected fall due to regression towards the mean. The regression towards the mean is also greater if \( \varrho \) is small. If \( \varrho \) were equal to 1, so that there were no measurement error whatsoever, the regression towards the mean would be zero. This formula would also apply if we took all subjects with blood pressure between two levels, e.g. diastolic between 90 and 100 mmHg.

The size of the regression towards the mean effect depends on the correlation \( \varrho \) between successive measurements \( x \) and \( y \) in the whole population. If \( x \) and \( y \) are measured within a few weeks, \( \varrho \) depends on the short-term variability of blood pressure. The correlation between short-term repeated measurements is also called the ‘coefficient of reliability’, and, following Shepard and Finison (15), we shall denote it by \( G \). We don’t know the value of \( G \) unless we measure a sample of the general population twice. Shepard and Finison use \( G \) in place of \( \varrho \) in the regression

\[ \text{Correlation coefficient (logarithmic scale)} \]

\[ \text{Years since initial examination} \]

\[ \text{Fig. 16. Correlation between initial systolic pressure and systolic pressure at subsequent examinations in Framingham Study (19).} \]
towards the mean equation, to give the regression effect as:

\[(1 - G) (\bar{x}_{hyp} - \bar{x}_{pop}).\]

However, blood pressure changes over time, and the longer the time interval between measurements \(x\) and \(y\), the smaller the correlation \(\rho\) between \(x\) and \(y\) will be. For both theoretical (18) and empirical (19) reasons, we expect that the correlation between initial and subsequent measurements of blood pressure will follow an exponential decay. Figure 16 shows such correlations for 18 years follow-up from the Framingham study, plotted on a logarithmic scale. The close fit to a straight line illustrates that the exponential model is reasonable.

Thus the correlation after \(t\) years is given by:

\[\rho = Ge^{-\lambda t}\]

where \(-\lambda\) is the slope of the regression line of \(\log \rho\) on \(t\). The long-term regression towards the mean effect is thus:

\[(1 - \rho) (\bar{x}_{hyp} - \bar{x}_{pop}) = (1 - Ge^{-\lambda t}) (\bar{x}_{hyp} - \bar{x}_{pop}).\]

We can estimate \(\rho\) in two ways. We can recall a random sample of our general population, including those without high blood pressure, and measure them again. This requires a moderately large sample, as correlation coefficients are hard to estimate accurately. To estimate a correlation coefficient of 0.8 to within 0.05 (95% confidence interval) requires a sample size of about 200 subjects. It has the advantage of applying to the population we are studying. The alternative approach is to use estimates of \(G\) and \(\lambda\) from existing data. Shepard and Finison (15) give estimates from the Framingham Study data (Table 6). As noted above, correlations are higher for systolic than for diastolic because the range is greater, and values of \(G\) show the same thing. Table 6 allows for taking the average of 2 or 3 measurements, and for averaging these over 2 or 3 visits. Shepard (18) gives estimates of \(G\) and \(\lambda\) for men and women separately. Averaging the estimates of \(\lambda\) to give estimates for men and women combined, we get \(\lambda = 0.020\) for systolic pressure and \(\lambda = 0.027\) for diastolic pressure.

These estimates are based on large samples, but may not apply strictly to another population. As a test of the applicability of Table 6, we calculated \(Ge^{-\lambda t}\) from the data of Hawthorne and colleagues (1), described above. For a single measurement of diastolic pressure, repeated after 1 year, we obtained \(\rho = Ge^{-\lambda} = 0.676\). Compare this to the value of \(G = 0.685\) from Table 6 and \(\lambda = 0.027\) giving \(Ge^{-\lambda t} = 0.685 \times e^{-0.027} = 0.667\). As Shepard and Finison quote 95% confidence intervals of \(\pm 0.01\) for their estimates, we can see that the two values of the correlation differ only by what could be ascribed to sampling error, despite the fact that the studies were conducted in different countries. Note that we cannot use the data of Table 1 to obtain an estimate of \(G\). These data were not a representative sample of blood pressures but obtained from a sample chosen to have high variation. Thus they will have an inflated correlation between repeated measurements and give too high a value of \(G\).
TABLE 6. Estimated coefficients of reliability (G) of average blood pressure, by number of visits and number of measurements per visit averaged (Shepard and Finison [15])

<table>
<thead>
<tr>
<th>No. of visits averaged</th>
<th>Systolic pressure</th>
<th></th>
<th></th>
<th>Diastolic pressure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Measurements at each visit</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>Measurements at each visit</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0.751</td>
<td>0.808</td>
<td>0.828</td>
<td>0.685</td>
<td>0.759</td>
<td>0.787</td>
</tr>
<tr>
<td>2</td>
<td>0.858</td>
<td>0.894</td>
<td>0.906</td>
<td>0.813</td>
<td>0.863</td>
<td>0.881</td>
</tr>
<tr>
<td>3</td>
<td>0.900</td>
<td>0.926</td>
<td>0.935</td>
<td>0.867</td>
<td>0.904</td>
<td>0.917</td>
</tr>
</tbody>
</table>

For an example, suppose that for the Hawthorne sample we choose all subjects with diastolic greater than 95 mmHg. Their mean is 103.3 mmHg and the mean for the whole population is 87.2 mmHg. We have a single measurement of blood pressure on one occasion, so from Table 6 the estimated value of $G$ is 0.685 and $\lambda = 0.027$, as above. The expected fall in mean pressure due to regression towards the mean is given by:

$$(1 - Ge^{-\lambda}) (\bar{x}_{hyp} - \bar{x}_{pop}) = (1 - 0.667) \times (103.3 - 87.2) = 5.4$$

Thus we would expect a fall of 5 mmHg in mean diastolic pressure, due to regression towards the mean.

In a randomized comparative study, the active and placebo or new and standard treatment groups would both experience regression towards the mean and so the effect would be cancelled out. Regression towards the mean would not affect the treatment difference. However, the apparent fall in pressure among patients receiving any treatment would be affected by regression effects and we can therefore estimate the true reduction in pressure using the method described here.

**Relating change to initial value**

A related issue arises when trying to study the relation between initial blood pressure and the change in blood pressure over time. In antihypertensive drug trials, for example, it may be postulated that the drug's effectiveness would be different (usually greater) for patients with more severe hypertension. This is a reasonable question, but unfortunately, as was shown above, the regression towards the mean will be greater for the patients with the highest initial blood pressures, so that we would expect to observe the postulated effect even in untreated patients. Another problem with using correlation to relate change to initial value (a common approach) is that for any two quantities $X$ and $Y$, $X$ will be correlated with $X - Y$. Indeed, even if $X$ and $Y$ are samples of random numbers, we would expect the correlation between $X$ and $X - Y$ to be 0.7. In other words, we expect to obtain a large correlation between initial blood pressure and the change in blood pressure even if the drug is ineffective and even if we do not restrict our study to hypertensives.

This problem was identified long ago, notably by Oldham (20), but it still causes difficulty (21). The simplest way around this problem is to take the average of the
initial and final measurement and calculate the correlation between this quantity and the observed change (20, 21). In the above notation this means correlating $(X + Y)/2$ with $X - Y$. If this correlation is large, it may reasonably be inferred that higher initial levels of the variable are associated with larger falls over time (or smaller rises). This analysis does not answer the posed question directly, however, and the analysis is based on some assumptions that are often unreasonable. In particular, it assumes implicitly that the variation (SD) among the initial and final blood pressures is the same, but this is unlikely given the method of selection. The best approach to this type of data is complex: further discussion is given by Wu and colleagues (22), Blomqvist (23), Hayes (24) and Vollmer (25). Again the method requires information about the population. There is more to this type of problem than is apparent, and statistical advice is recommended.

APPENDIX: FORMULAE FOR THE SLOPE OF THE REGRESSION LINE

The expression for a regression line given in the text:

$$y = \mu_y + q \frac{\sigma_y}{\sigma_x} (x - \mu_x)$$

is consistent with the familiar $y = a + bx$ (4, 26). The estimates of $q$, $\sigma_x$, $\sigma_y$, $b$ and $a$ are:

$$\hat{q} = \frac{\Sigma(x_i y_i - \bar{x} \bar{y})}{\sqrt{\Sigma(x_i - \bar{x})^2 \Sigma(y_i - \bar{y})^2}}$$

$$\hat{\sigma_x} = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{n - 1}}$$

$$\hat{\sigma_y} = \sqrt{\frac{\Sigma(y_i - \bar{y})^2}{n - 1}}$$

$$b = \frac{\Sigma(x_i y_i - \bar{x} \bar{y})}{\Sigma(x_i - \bar{x})^2}$$

$$a = \bar{y} - b \bar{x}$$

where $x_i$, $y_i$ are the observations and $n$ is the sample size. If we divide $\hat{q}$ by $\hat{\sigma}_x$ and multiply by $\hat{\sigma}_y$ we get $b$. We note that $\bar{x}$ is an estimate of $\mu_x$ and $\bar{y}$ is an estimate of $\mu_y$ and put these into the equation for $a$ to see that the two forms are equivalent.
REFERENCES


16. Direct measurement of blood pressure

John N.W. West, James J. Sheridan and William A. Littler

The first documented recording of direct arterial blood pressure is the description by the Reverend Stephen Hales in 1733 of his cannulation of a neck artery in a horse and his observation of the height of the resulting column of blood in a glass tube (1). The first arterial blood pressure measurement in a human, by Faire in 1856, was also performed by direct arterial cannulation (2). This, however, was not a practicable method of routine clinical assessment and following the descriptions of Hill and Barnard (3) in 1898, Riva-Rocci (4) in 1896 and Korotkov (5) in 1905, cuff-occlusion techniques of indirect arterial blood pressure determination became universally adopted (see Chapter 1). These non-invasive techniques had the advantages of being easy to learn, easy to perform, readily repeated at regular intervals, requiring relatively simple equipment, and causing minimal discomfort to the patient.

With the rapid expansion of cardiac surgery in the 1950s and 1960s there arose a need to be able to monitor rapid fluctuations in blood pressure in hemodynamically unstable individuals and to measure blood pressure during periods while the patient was on cardiopulmonary bypass, a time when blood flow is non-pulsatile. This need could be met by applying modern strain-gauge technology first used for direct intra-arterial blood pressure measurement by Lambert and Wood (6). Thus was ushered in the modern era of intra-arterial blood pressure recording, which transformed the management of the acutely ill patient. The technology was applied by Bevan and colleagues (7) in 1969 to the measurement of blood pressure in the ambulant patient, a development which has permitted a considerable expansion of our knowledge of blood pressure behavior in normal and hypertensive individuals.

The fundamental difference between non-invasive and direct measurement of blood pressure is the ability of the latter to give a continuous record of blood pressure, whereas most non-invasive techniques can necessarily only provide intermittent measurement. The possible loss of accuracy that occurs with non-invasive measurement of blood pressure is probably not of clinical significance in most patients, but may be of great importance in a minority of 'difficult' cases. Measurements of direct arterial pressure, however, differ importantly from non-
invasive measurement by Korotkov sound detection which probably slightly underestimates systolic pressure and overestimates diastolic pressure (8).

Acceptable systems for long-term monitoring of intra-arterial pressure have been developed over the last 30 years, with the miniaturization of the equipment to allow unrestricted activity the most important advance. The miniaturized system developed by the Oxford group (9) was the first to permit true ambulation, with data stored in analog form initially on photographic plates, and subsequently on magnetic tape.

I. INTRA-ARTERIAL CANNULATION: TECHNIQUE

The non-dominant brachial artery is most commonly used, although the technique described can be applied to other peripheral arteries, notably the radial artery (10). The intra-arterial catheter is inserted under aseptic conditions using the Seldinger technique (11). The subject is placed in a recumbent position with the non-dominant arm extended at the elbow and rested on a horizontal surface. The brachial artery is identified by palpation and the cannulation site is chosen, usually 1 cm above the antecubital crease (Figs. 1 and 2). The skin is prepared with antiseptic (chlorhexidine) and infiltrated with 2–5 ml of 1% lignocaine. The artery is punctured percutaneously using a 3-French (1 mm diameter) needle inserted at an angle of 45° to the skin surface (Fig. 3). Correct positioning is ensured by observing a free flow of arterial blood from the needle. A fine guidewire is threaded through the needle, care
being taken to avoid forcing the guidewire against resistance. The needle is then removed, and a catheter threaded over the guidewire to lie in the arterial lumen (Fig. 4). On removing the guidewire, the catheter is connected via Teflon connecting tube to the transducer – perfusor system. Special care is necessary to ensure that no air

Fig. 2. The commonest site for cannulation of the brachial artery is 1 cm above the elbow crease. A = Seldinger needle; B = brachial artery.

Fig. 3. The Seldinger technique. (1) Artery punctured precutaneously at an angle of 45° to the skin, ensuring a good flow back of arterial blood. (2) The Seldinger wire is threaded through the needle. A = Seldinger wire.
Fig. 4. The Seldinger technique. The needle is withdrawn over the Seldinger wire and the cannula advanced into the vessel. A = Seldinger wire; B = intra-arterial cannula.

bubbles are introduced into the system. The catheter insertion site is then covered with a sterile padded dressing secured with elastic adhesive tape.

Removal of intra-arterial cannulae

On removing the catheter, it is important to maintain pressure over the arterial puncture site for at least 10 minutes to achieve secure hemostasis. Ideally, hemostasis should be the responsibility of the physician who inserted the cannula, and should not be delegated. After hemostasis has been achieved, a pressure bandage is applied. The patient should rest with the arm slightly elevated for 1 hour. The radial and ulnar pulses should be palpated to ensure vessel patency. The patient is advised to avoid excessive use of the arm (e.g. heavy lifting) for a further 24 hours.

II. THE 'OXFORD' AMBULATORY BLOOD PRESSURE RECORDING SYSTEM

The apparatus consists of a catheter, connecting tube, transducer, perfusion pump and tape recorder (Fig. 5). The apparatus is based on the original design of Stott and Bevan (9), working in Sir George Pickering's department at Oxford. The catheter consists of a fine (3-French or 1.03-mm external diameter) Teflon catheter 10 cm in length (Grand-Jean arteriocath-3, Plastimed BP 20.95, Saint Leu-le-Foret). This is attached via a 1 meter length of fine teflon connecting tubing to the transducer — perfusor system (Romulus Mk III). The transducer is a semi-conductor strain gauge device. The perfusor consists of a reservoir of 35 ml capacity and a peristaltic pump which is driven by mercury batteries to perfuse the system with sterile water (not saline — to avoid corrosion of components) containing a small amount of heparin (100 U/100 ml) at a rate of 2 ml/h. The transducer is further connected to a recording system consisting of a miniaturized 4-channel analog tape recorder first described by Marson and McKinnon (12) and manufactured by Medilog Ltd. (Oxford Instruments) containing a standard 120-minute magnetic tape cassette played at a slow recording speed (2 mm/s). The slow recording speed is very
Fig. 5. The Oxford ambulatory intra-arterial blood pressure recording apparatus. The perfusor/transducer apparatus is shown to the right, the recorder to the left. Also shown are leads for electrocardiographic and event channel recordings.

demanding on the mechanics of the cassette, which has to be of high quality. The 4 available channels are separated to avoid the possibility of cross-talk. In practice, 3 of the available channels are used: blood pressure, heart rate and a time/event channel.

The transducer—perfusor system and the connecting tube are first thoroughly sterilized with a disinfectant preparation of glutaraldehyde 2% activated with 0.3% sodium bicarbonate (‘Cidex’) which is flushed out of the apparatus using sterile water.

The transducer—perfusor system is placed in a padded harness worn at heart level, taken as the zero reference point for arterial pressure. Care is taken to avoid kinking the connecting tube, which may introduce damping into the recording. The recording system is also carried in the chest harness. It is important to ensure that both the transducer—perfusor system and the connecting tube have first been thoroughly sterilized with a disinfectant preparation of glutaraldehyde 2% activated with 0.3% sodium bicarbonate (Cidex) and that all traces of the Cidex have been flushed out of the apparatus using sterile water. The persistence of a green tint in the fluid reservoir or connecting tube should alert the operator to the residual presence of the disinfectant.
Calibration

The transducer is calibrated using a mercury manometer connected via a 3-way tap. The manometer pressure is raised stepwise in 50-mmHg increments. A properly calibrated device has been shown to accurately measure blood pressure over the range 30 – 270 mmHg (13). Special care must be taken at this stage to ensure that the 3-way tap is left in a position to prevent accidental injection of air into the patient's artery from the manometer bulb. A specially-designed 3-way tap incorporating a safety catch is fitted to prevent this possibility.

Subjects undergoing measurement of direct arterial pressure by this method are asked to report immediately any problems related to the catheter, to avoid any excessively strenuous activity likely to damage or displace the apparatus and to avoid allowing the instruments to come into contact with water. Due to the limited capacity of the fluid reservoir, the water/heparin mixture is replenished within 20 hours of recording.

Analysis of data

The tape cassette is replayed on a playback system (Oxford Instruments) at 60 times normal speed. Fast data reduction of blood pressure recording data was introduced by Cashmann and Stott (14). The signal can be converted into a simultaneous oscilloscope display and recorded on a pen chart paper recorder. The recording should be screened by an experienced observer to identify artefactual recordings, such as pump artefact, which can occur when the catheter tip becomes lodged against the vessel wall, leading the damping of the trace and transmission of artefact from the roller pump in a cyclical fashion, an example shown in Figure 6. The data thus screened are digitised and stored in a computer for analysis.

Accuracy

The Oxford system has been evaluated for accuracy in terms of frequency and square wave responses, linearity over the range 0 – 300 mmHg, zero shift, gain change and noise level and constancy of tape speed by Goldberg and colleagues (13). The system was found to record arterial pressure accurately with a calculated damping ratio of 0.75 and an overshoot of 15% in the hydraulic components. Linearity was maintained to static pressure testing over the middle two-thirds of the range 0 – 300 mmHg with decreased responsiveness at each end. The tape speed was accurate with a coefficient of variation of 0.5%. Only 1 – 2% of the pulse widths in Millar-Craig and colleagues' analysis (15) were found to have an error exceeding 20 ms, the majority of these occurring at the extreme ends of the tape. The physical characteristics of the entire system were found to be accurate up to 8 Hz; it was therefore concluded that the Oxford apparatus was accurate for pressure measurement but not for wave form analysis.

Logan (16) observed temperature-induced errors in the pressure records, a finding which was not confirmed by Goldberg (13) or Millar-Craig (17). Kenny and colleagues (18) suggested that temperature-induced error was more likely when battery power was failing.
Fig. 6. An example of recording artefact induced by excessive tortuosity within the brachial artery, with a normal recording shown on the right.

III. METHODS OF DISPLAYING 24-HOUR BLOOD PRESSURE DATA

Large amounts of data are produced in each 24-hour ambulatory study. Data reduction presents a considerable challenge, requiring the memory capacity of a mini-computer system (our laboratory currently uses a Nova 3-mini-computer, Data
General, Southboro, MA, U.S.A) to achieve full digitization of the analog signal. Recognition of artifact is achieved by rejection of signals with an upstroke of less than dp/dt 7 mmHg in 20 ms (19). Other workers (13) have used the presence of a dicrotic notch to confirm the presence of a true arterial upstroke. The indices derived in these studies are values of systolic and diastolic pressure and beat-to-beat interval (pulse interval). These data are subdivided into timed blocks, each block of data representing recordings over approximately 7 minutes. Most centers employing the technique display data as hourly averaged blood pressure and heart rate throughout the recording period. West (20), working with the Oxford group, first described the use of frequency histograms and standard deviation histograms to illustrate both the median blood pressure and the total spread of data during the recording period.

An example of a frequency histogram plot obtained from an untreated patient aged 18 years before and 6 weeks after operative correction of co-arctation of the aorta is shown in Figure 7.

Continuous records of ambulatory blood pressure and heart rate can be produced using an ultraviolet paper recorder, so that an additional permanent visual record is obtained. These records are particularly useful for correlation of the blood pressure signal at times when the event channel is activated.

![Figure 7](image-url)

**Fig. 7.** Analysis of data from the Oxford intra-arterial apparatus. Frequency histograms of systolic blood pressure (SBP) and diastolic pressure (DBP) from a patient studied before (solid lines) and 6 weeks after (interrupted) surgical correction of a co-arctation of the aorta.
IV. MEASUREMENT OF DIRECT ARTERIAL PRESSURE: CLINICAL APPLICATIONS

Derivatives of Bevan's original system for monitoring of direct arterial pressure have been applied by several different groups, and have allowed comprehensive study of normal blood pressure behavior in a variety of physiological situations including free ambulation (21, 22), normal sleep (23 – 25), defecation and micturition (26), coitus (27, 28), cigarette smoking (29) and motor car driving (30).

Measurement of direct arterial pressure has contributed significantly to our understanding of 24-hour blood pressure behavior in the unrestricted and ambulant patient. Among many other findings are the large variations between intra-arterial blood pressure and clinic sphygmomanometric pressure measured by a physician, an effect observed by Mancia (31) and Littler (32). One important difference between the behavior of the directly measured intra-arterial pressure and clinic measured blood pressure is the absence of any recorded placebo effect on blood pressure reduction (33, 34). Whether this phenomenon relates to the effect of a substantial number of readings (more than 85000 systolic beats occur in a 24-hour period) reducing the degree of regression to the mean is unsubstantiated. Blood pressure measurements recorded by this technique have been shown to have a high degree of reproducibility (35) in addition to the absence of placebo effect.

The diurnal variation in blood pressure

One of the first uses of continuous recordings of intra-arterial pressure has been to confirm the striking changes in arterial pressure that occur in association with physical activity and sleep. Whether these changes reflect a chronobiological phenomenon due to an intrinsic circadian rhythm of blood pressure homeostasis, as suggested by some workers (36), or whether they reflect simply a diurnal pattern related to the degree of physical activity and effect of sleep (37), has been the subject of some debate. The balance of evidence seems to support a diurnal variation with physical activity and sleep the major determinants of the level of arterial pressure in a given individual.

Borderline or 'white coat' hypertension

The usefulness of direct arterial pressure recording in detecting patients with an exaggerated 'defence reaction' was demonstrated (32) in a group of patients whose clinic blood pressure measurements appeared disproportionately high. Many of these patients were found to have a marked pressor response to attending hospital, and relatively normal levels of arterial pressure while at home. Mancia's study (31) of intra-arterial recording in hospitalized patients presenting with similarly high casual blood pressure readings confirmed the pressor effect (which averaged 27 mmHg systolic and 15 mmHg diastolic pressure rise) of the presence of the physician in these patients.
Event marking

The facility to allow patient-activated event marking during the recording of direct blood pressure permits a clinician to correlate symptoms and the exact blood pressure level at the time. This facility, analogous to event marking during Holter monitoring for cardiac arrhythmias, is of particular use in patients with unexplained syncope or 'funny turns' of uncertain etiology. It is known, for example, that episodes of postural hypotension in autonomic failure can be short-lived and are not always associated with symptoms (38). An example of an intra-arterial pressure recording showing profound circulatory changes during a spontaneous Valsalva maneuver at the time of defecation in a 73-year-old man is shown in Figure 8.

Autonomic failure

In the laboratory setting, the use of intra-arterial cannula connected to a perfusing system to ensure patency, transducer and high-fidelity recording apparatus facilitates accurate recording of blood pressure and heart rate on a beat-by-beat basis. Assessment of autonomic activity in patients is greatly facilitated by recording of direct arterial pressure and heart rate during standardized challenges to the circulation such as prolonged head-up tilting — for a minimum of 15 minutes as shown by Fitzpatrick (39), — facial immersion, cold pressor test, and Valsalva’s maneuver. Interpretation of intra-arterial records in terms of clinical diagnosis of autonomic dysfunction in these circumstances has been described by Bannister and colleagues (40).

Ambulatory recording of direct arterial pressure has proved useful in the diagnosis of autonomic dysfunction syndromes and in the assessment of drug treatment of autonomic failure. Mann and colleagues (38) noticed a characteristic pattern of inversion of the normal pattern of diurnal variation of blood pressure com-

![Graph](image)

Fig. 8. Analysis of data from the Oxford intra-arterial apparatus. Profound effects on intra-arterial blood pressure induced by a spontaneous Valsalva maneuver during defecation in a 73-year-old man.
bined with a marked reduction of normal heart rate variability. In a study (41) of patients with advanced autonomic failure due to the Shy Drager variant of multiple systems atrophy, short-lived episodes of severe postural hypotension combined with severe hypertension in the fully supine position were noted in untreated patients. Following treatment with a partial $\beta$-adrenoceptor agonist, exaggeration of the episodic severe supine hypertension was recorded, but these episodes may have been too short-lived and infrequent to have been registered by conventional intermittent recording techniques.

**Relationship between direct arterial pressure measurements and prognosis in hypertension**

Suggestions that prolonged ambulatory recording of blood pressure may produce a more representative signal on which to base prognostic information has been made (25, 42) and this has been supported by a study of ambulatory blood pressure recorded using a non-invasive automatic sphygmomanometer device (43, 44). Whether direct ambulatory blood pressure itself relates to prognosis is uncertain, although Mann and colleagues (45) showed that, with a small number of subjects, intra-arterial records demonstrated superior prognostic capability compared with clinic measurement. It is unlikely that this finding will become any more firmly established because of insufficient numbers of patients studied.

It has been suggested, however, that other components of the blood pressure profile not revealed by either repeated measurement or casual measurement may be important. Pattison (46) suggested that the highest point of the blood pressure achieved by an individual was more likely to be damaging than sustained high blood pressure, whereas others have taken the opposing view that the basal blood pressure is more predictive of future cardiovascular risk (47).

The potential difficulties with obtaining a representative casual blood pressure, whether this represents a basal level or reflects the highest point, or interpretation of an automatically recorded ambulatory blood pressure level has led to the use of other ‘pressure-independent’ measures of prognosis in the assessment of an individual presenting with a high clinic blood pressure reading. The obvious advantage in measurement of prognostic variables is their independence from the artefact that can be induced by casual clinic blood pressure measurement. In common use are measures of left ventricular hypertrophy, both from electrocardiography and echocardiography. Both measures of left ventricular hypertrophy have been shown prospectively to relate to future cardiovascular risk (48, 49).

The relationship between echocardiographically defined left ventricular mass and blood pressure level has been described by several authors and reviewed by Devereux and colleagues (50) (see Chapter 14). Most authors have used linear regression analysis between clinic blood pressure and echocardiographic left ventricular mass defined by numerous formulae. A few studies exist describing the relationship between ambulatory recording of direct arterial pressure and echocardiographic left ventricular mass; two groups (51, 52) have described a statistically significant correlation between ambulatory intra-arterial blood pressure and echocardiographic left ventricular mass.
V. MEASUREMENT OF DIRECT ARTERIAL PRESSURE: RESEARCH APPLICATIONS

Direct arterial pressure during sleep

The ability to record blood pressure on a beat-by-beat basis during undisturbed sleep remains a substantial advantage of intra-arterial systems. None of the current non-invasive sphygmomanometric techniques can allow truly undisturbed sleep because of the effect of cuff inflation. MacWilliam (53) drew attention to the high incidence of cerebral hemorrhage and angina attacks during sleep, and postulated autonomic lability during dreaming. However, a study by Shaw and colleagues (54) using non-invasive recording of blood pressure over 24-hour periods did not show that hypertensive patients with cerebral ischemia had increased blood pressure lability compared with controls. This pattern was confirmed by others (55) using similar methodology. Their findings may have been due to the 10–30 minute recording intervals used during sleep which may have been insufficient to detect short-lived lability. Intra-arterial records can be regarded as showing a more definitive record of blood pressure patterns during normal sleep and have shown that, although blood pressure during sleep is lower than during physical activity (36, 37), at certain times sleeping blood pressure can demonstrate quite marked lability.

Littler’s study (25) of direct arterial pressure during sleep comparing normotensive and both treated and untreated hypertensive subjects showed that all 3 groups had equal falls, of the order of 20%, in blood pressure during sleep compared with the waking pressure level. This fall was of the same magnitude, suggesting that the hypertensive subjects did not have higher centrally induced vasoactivity and that antihypertensive drugs did not appear to alter the pattern of blood pressure behavior induced by sleep.

Measurement of baroreflex activity

Smyth and colleagues (56) described a technique for quantifying baroreceptor sensitivity in human subjects by measuring the beat-by-beat reflex cardiac slowing that occurred following injection of pressor agents. A linear relationship between heart rate and blood pressure during the rise in blood pressure was demonstrated using a regression plot of the two variables, in which the slope of the regression line was used as an index of the sensitivity of the complete baroreflex arc. Smyth’s technique requires intra-arterial cannulation for accurate beat-by-beat measurement of blood pressure and is still widely applied in clinical research. More recently, different groups (57, 58) have analyzed patterns of spontaneous beat-by-beat co-variation of systolic blood pressure and pulse interval, using ambulatory intra-arterial recordings to overcome the intermittent nature of conventional baroreceptor analysis. Many hundreds of such sequences were identified (58), with fewer sequences seen in hypertensives who also showed a significantly lower baroreflex sensitivity.

Validation of alternative techniques for blood pressure measurement

Most current validation procedures assess the accuracy of a blood pressure measure-
ment device against a known standard, most commonly a mercury sphygmomanometer. It is recommended that blood pressure is measured simultaneously in the same arm as the test device using standard sphygmomanometry, with blinded observers (American National Standard for Electronic or Automated Sphygmomanometers, Association for Advancement of Medical Instrumentation) (59) and British Hypertension Society recommendations (60). However, in practice it may be difficult to achieve a truly simultaneous measurement in the same arm due to a number of technical factors: many devices release cuff pressure so rapidly that an observer is unable to auscultate accurately.

Some authors have attempted validation procedures by comparison with simultaneous intra-arterial pressure. Gould and colleagues (61) measured intra-arterial pressure during free ambulation in hospital outpatients using the Oxford system and a Remler M2000 recorder. A patient-activated event marker was used to identify the exact timing of the automated recorder measurements. Casadei’s study (62) of the Spacelabs 5300 recorder used similar methodology, relying on the time of cuff inflation (15 minute intervals with known start time) to obtain the signal from the Oxford system. Winberg and colleagues (63) used simultaneous intra-arterial recording in a laboratory setting to show that automated recorders using the oscillometric principle (Takeda 751) and the Korotkoff-sound-based principle (Copal 251) produced comparable accuracy, refuting the suggestion (64) that oscillometric methods were superior to auscultatory readings in automated recorders.

Pomidossi and colleagues (65) used the Oxford intra-arterial system simultaneously with a Vita-Stat 901 recorder, in a laboratory setting, to determine whether the cuff inflation itself provoked an ‘alarm reaction’ as judged by a rise in blood pressure and heart rate at the time of cuff inflation. No such reaction was observed, either when the cuff was automatically inflated or self-inflated by the patient.

Effects of drug treatments in hypertension

By virtue of its reproducibility and absence of observer bias or any demonstrated placebo effect, intra-arterial recording has previously been recommended as the optimum method for the assessment of antihypertensive drugs (66). Valuable information on the clinical pharmacology of various antihypertensive agents has been obtained by numerous centers for the main classes of antihypertensive agents. \(\beta\)-Adrenoceptor antagonists, particularly, have been studied in detail (67).

VI. ETHICAL CONSIDERATIONS

Any technique involving intra-arterial cannulation is associated with potential cardiovascular risk to the patient. Recording of direct arterial pressure should only be performed in a suitable laboratory environment by experienced medical and technical staff. It is our policy to obtain formal written consent from all patients undergoing intra-arterial cannulation. As studies are generally performed to improve rather than achieve diagnosis, any difficulties encountered in insertion of the intra-arterial needle such as patient discomfort, vaso-vagal reaction or difficulty in obtaining satisfactory arterial flowback, necessitates abandoning the study.
Patients in whom intra-arterial access is required for other medical reasons (e.g. frequent measurement of arterial blood gases) present less of an ethical issue, but in this setting both physician and patient (where possible) should have a full appreciation of the possible complications of intra-arterial cannulation, and informed written consent should be obtained.

In- or outpatient studies

Most of the studies of intra-arterial ambulatory recordings have been performed on hospital out-patients who are asked to re-attend the hospital so that the equipment can be calibrated, the reservoir refilled and the cannula site inspected. Activity diaries are kept, and many studies are performed using standardized activity protocols (37). Standardization of activity is particularly important in studies of the pharmacokinetics of antihypertensive drugs.

Careful selection of patients is necessary to ensure that outpatient monitoring is appropriate. It is our policy to conduct studies in hospital in those patients with severe hypertension (arbitrarily defined as a resting systolic intra-arterial pressure exceeding 200 mmHg), patients with suspected autonomic insufficiency and in those patients without access to transport to hospital.

VII. COMPLICATIONS OF THE TECHNIQUE

Arterial cannulation is associated with a documented appreciable morbidity (68). However, most centers routinely performing intra-arterial measurement of blood pressure have reported that significant complications are exceedingly rare. The Northwick Park group (69) in a clinical audit of 1000 cases of intra-arterial cannulation including cases where multiple cannulations had been performed in the same patient reported one major complication — an infected pseudoaneuysm of the brachial artery (as described previously by Wagner (70) — with a small proportion of minor complications including local hematoma formation (4 – 5%), hemorrhage (1 – 2%), discomfort at the insertion site (3%) and vaso-vagal reaction at insertion of cannula (1 – 2%).

Median nerve compression by hematoma formation deep to the biceps tendon aponeurosis has been recorded with the Oxford technique (71), as well as other techniques (72, 73). It is recommended in these cases that early surgical decompression of the median nerve is performed.

Reduction in distal pulsation is a documented complication of intra-arterial cannulation. Bedford and Wollmann (74) described a 40% incidence of radial artery thrombosis following prolonged radial arterial cannulation; all that were followed, however, recanalized spontaneously. Other studies report a varying incidence of pulse reduction following brachial artery cannulation (usually performed during cardiac catheterization in which larger diameter catheters are used): e.g. Barabas (75) 4%, Campion (72) 6%, Karmody (76) 6%.

Embolic phenomena are a further recognized complication of the procedure. Most reports suggest the possibility of fibrinous or platelet emboli, with reports of
larger emboli being very uncommon. Abrams (77) reported 1 case where septic emboli affected 4 fingers, Matthews and Gibbons (78) reported a single case of septic embolus following brachial artery needle puncture and Michaelson and Walsh (79) reported the appearance of an Osler’s node associated with an indwelling arterial catheter and associated bacteremia.

VIII. SUMMARY AND CONCLUSIONS

The wider applicability of non-invasive ambulatory recorders of blood pressure will probably supersede the measurement of direct blood pressure in the identification of patients with borderline hypertension or an exaggerated defence reaction (‘white coat hypertension’), and in studies of drug treatment of hypertension. This is subject to the important proviso that a standard method of the validation of these machines is accepted. Direct measurement of blood pressure is therefore likely to be limited to the assessment of blood pressure levels in a patients with unusual disorders of blood pressure control or as a research tool. A major advantage in the management of difficult cases is the ability to produce a continuous record of direct blood pressure during physiological activity such as standing, sitting, sleeping and unrestricted physical activity.

Measurement of direct arterial pressure will continue to have a role in cardiovascular research. It remains a useful technique in the management of difficult patients or where extremes of blood pressure are likely to be encountered. The facility to allow event marking during symptomatic episodes is not available on current non-invasive monitoring equipment, and this allows analysis of any correlation between symptoms and the simultaneous blood pressure level. Measurement of direct arterial blood pressure continues also to have a role in the diagnosis and in the monitoring of patients with suspected dysfunction of the autonomic control of blood pressure.

REFERENCES


17. Blood pressure measurement and monitoring in anesthesia

A.J. Cunningham and A. Synnott

I. INTRODUCTION

Historical perspectives

The measurement of arterial blood pressure is generally acknowledged to be one of the most valuable physiological measurements in clinical anesthesia. Intraoperative measurement of arterial blood pressure in humans was first performed in 1903 by a medical student, Harvey Cushing, a portent of future distinctions (1). However, a Committee of his Professors at the Massachusetts General Hospital, in a report published in 1904, found little value in this practice. Subsequent developments were to confound Harvey Cushing's critics. Over the past 3 decades, perioperative cardiovascular monitoring has progressed from finger on the pulse and indirect blood pressure monitoring techniques (1950s) to direct invasive blood pressure monitoring in the 1970s and automated oscillometry devices in the 1980s.

Physiological principles

Pressure changes in the arterial system are dependent on the product of two factors — the volume of blood ejected by the ventricular per unit time, i.e. the cardiac output, and the resistance to blood flow offered by vessels in the peripheral vascular bed. Resistance of a blood vessel, in turn, varies inversely with the fourth power of its radius. At any given level of cardiac output arterial pressure is therefore dependent on the degree of arteriolar smooth muscle contraction. These physiological functions may be altered by changes in humoral and autonomic nervous system activity and their effects on the heart and the systemic vascular resistance (2). Although resistance to blood flow varies with the viscosity of blood and the length of the vessels, alterations in these factors are normally only of secondary importance.

Disturbances of arterial pressure are primarily sensed by the arterial baroreceptors, located in the carotid sinuses and the aortic arch. An increase in arterial pressure causes increased baroreceptor firing, and provokes inhibitory reflex
responses mediated by decreased sympathetic outflow and increased vagal activity. Conversely, decreased arterial pressure results in decreased baroreceptor discharge causing increased sympathetic nervous system activity.

'Long term' arterial pressure control is closely linked with control of body fluid volumes and involves the kidneys and other organs which regulate the water/electrolyte balance (3). The kidney regulates arterial pressure by modifying the excretion of water and sodium, partly through direct, pressure-linked, natriuresis, partly through the renin–angiotensin–aldosterone system (RAS), partly through the excretion of antidiuretic hormone and, to an undetermined extent, by the release of atrial natriuretic peptide (4).

Anesthesia and the hypertensive patient

Drugs administered in the perioperative period and consequences of tracheal intubation and mechanical ventilation may alter, independently or together, the control of blood pressure by their effects on cardiac output, systemic vascular resistance, autonomic nervous system activity, regional end-organ blood flow, endocrine function and reflex baroreceptor activity. Patients with untreated hypertension may exhibit exaggerated pressor responses to stimuli, e.g. pain, laryngoscopy and intubation, which evoke sympathetic nervous system activity and exaggerated hypertensive responses to induction and maintenance of anesthesia (5). Because of the association of hypertension and coronary artery disease, such hypertensive responses to noxious stimuli may be accompanied by evidence of myocardial ischemia (6). Pre-existing hypertension may increase the occurrence of postoperative myocardial infarction in patients with a history of previous myocardial infarction. Hypertensive response to laryngoscopy and tracheal intubation is particularly susceptible to β-adrenoceptor blockade (7). In untreated or poorly controlled hypertensive patients, during maintenance anesthesia, the changes in arterial pressure from the awake state are greater than those observed in normotensive patients. Occasionally exaggerated hypertensive responses may occur in inadequately treated hypertensive patients following the termination of anesthesia (8).

This contribution will concentrate on the changes in blood pressure during anesthesia and surgery, manipulation of blood pressure (deliberate hypotension and induced hypertension) in the perioperative period and an assessment of direct and indirect blood pressure monitoring techniques.

II. CHANGES IN BLOOD PRESSURE DURING ANESTHESIA AND SURGERY

Drug effects

Changes in arterial pressure which occur during anesthesia and surgery are a composite of the direct hemodynamic effects of the anesthetic agent and ventilatory support system employed, the reflex hemodynamic responses to such changes in arterial pressure, and the nature and extent of noxious stimuli associated with the particular
surgical procedure. Studies in human volunteers permit the isolation of anesthetic effects from those of disease, surgery, and the concomitant pharmacological and physiological intervention.

Rapid injection of the commonly used intravenous induction agents, with a notable exception of ketamine, in doses sufficient to abolish the eyelash reflex and to induce loss of consciousness, causes decreases of both systolic and diastolic arterial pressures. The reduction in arterial pressure may be due to a combination of reduced cardiac output and systemic vascular resistance (9). The degree to which either of these variables change depends on the degree of reflex increase in heart rate and the degree of venous dilatation. The extent of arterial pressure reduction depends on the agent used and the dose and rate of drug administration.

The commonly used intravenous induction agent thiopentone is associated with a dose-dependent depression of myocardial contractility and cardiac output, decreased venomotor tone, with relatively unchanged systemic vascular resistance. These cardiovascular effects are due to both a central nervous system action and, to a lesser degree, a direct action on venous smooth muscle tone. The decrease of arterial pressure associated with the commonly used intravenous induction agent thiopentone, methohexitone, midazolam and etomidate are accompanied by substantial increases in heart rate. The increased heart rate commonly associated with intravenous induction agents may be due to a central release of vagotonic control of heart rate. The sensitivity of the reflex baroreceptor control of heart rate is usually, with the exception of propofol (10), depressed by anesthetic agents, so that the increased heart rate observed is unlikely to be due to baroreceptor reflex response to the decreased arterial pressure. In contrast with other intravenous induction agents, the dose-related increase in arterial pressure and heart rate produced by ketamine may be due to central nervous system stimulation, resulting in peripheral vasoconstriction and increased heart rate (11).

Laryngoscopy and tracheal intubation

Laryngoscopy and tracheal intubation are potent stimuli which may produce activation of the autonomic nervous system and which may be associated with significant increases in heart rate, arterial blood pressure, intracranial and intraocular pressure (12). The hemodynamic responses to laryngoscopy and intubation represent a balance between the noxious stimuli involved and their suppression by the intravenous anesthetic agent and the direct central nervous system and cardiovascular-system-depressant effects of the anesthetic agents involved. Poorly controlled or untreated hypertensive patients may be particularly prone to significant hypertensive responses to laryngoscopy and intubation (7). Attenuation or avoidance of pressor responses to laryngoscopy and intubation is generally desirable and mandatory in patients with ischemic heart disease and cerebral vascular anomalies. Measures available include continuation of preoperative β-adrenoceptor blockade, either administered orally before anesthesia or intravenously at the time of induction of anesthesia, and the presence of a sufficiently deep level of anesthesia following intravenous or inhalation anesthetic administration.

In patients where the depression of cardiac output attending deep levels of conventional volatile anesthetic agent is especially hazardous, a technique of high-dose
narcotic anesthesia may have a role in that the hemodynamic responses to laryngoscopy/intubation may be attenuated.

**Maintenance of anesthesia**

The modern inhalation anesthetic agents halothane, enflurane and isoflurane all decrease mean arterial blood pressure in direct proportion to the inspired concentration administered. In contrast, many of the older anesthetic agents which have now fallen into disfavor (e.g. diethyl ether and cyclopropane) had little effect on arterial pressure even in high concentrations.

Halothane reduces cardiac output and its effect parallels the effect on arterial pressure. Because systemic vascular resistance is unchanged with halothane, the reduction in cardiac output is due to depressed myocardial contractility (13). Enflurane also reduces cardiac output and its effect also parallels its effects on arterial pressure (14). However, with this agent, systemic vascular resistance is reduced and myocardial contractility is depressed. In contrast to the other commonly used inhalation anesthetic agents, isoflurane is associated with an unchanged cardiac output and a reduced mean arterial pressure associated with lower systemic vascular resistance (15). Isoflurane-induced arterial hypotension is associated with increased heart rate which reflects the lack of depression of baroreceptor reflex sensitivity in comparison with halothane or enflurane.

**Regional anesthesia**

Spinal and epidural anesthesia results in temporary sympathectomy of the part of the body blocked. The extent of sympathetic blockade generally exceeds that of pain block by several spinal segments. Thus, a spinal anesthetic, administered for a transurethral prostatectomy resulting in a sensory block up to the level of T8, may be associated with sympathetic blockade to the level of the upper thoracic dermatomes. Such a sympathetic block will result in profound vasodilation below the level of the block. The effect on blood pressure will depend on the extent of compensatory vasoconstriction above the block and ability to increase cardiac output in the face of a drop in afterload. If the sympathetic block extends above T4, the sympathetic supply of the heart is cut off, further compromising compensatory response. The onset of spinal anesthesia, with its associated cardiovascular changes, is rapid. Spinal anesthesia is generally established within 5–10 minutes of injection of the local anesthetic agent. In the case of epidurals, the onset is slower — perhaps 20–30 minutes and more controllable. In other regional techniques which necessitate use of very large volumes of local anesthetic agents (e.g. bracial plexus blocks), the blood levels of local anesthetic agents produced may cause significant myocardial depression.

Regional techniques are far from innocuous as indicated by their effects on the cardiovascular system. Thus, they call for the same elaborate monitoring and resuscitation equipment and techniques being available as for general anesthesia. Moreover, as the hemodynamic effects of regional techniques are less predictable and controllable than those of general anesthetic techniques, the latter approach is generally preferable in patients with significant cardiovascular disease.
Surgical stimuli

A number of surgical interventions may produce significant alterations in arterial pressure during surgery. In ophthalmic surgery the oculocardiac reflex caused by traction on the extraocular muscles, ocular manipulation or pressure on the globe may be manifest by profound bradycardia and hypotension (16). Small bowel evisceration, traction on the visceral or parietal peritoneum, manipulation of the bladder or common bile duct, and traction on the mesentery may all cause reflex sympathetic responses characterized by tachycardia, hypertension, sweating and cutaneous pallor. These reflex cardiovascular responses to surgical stimuli may be attenuated or prevented by deep levels of anesthesia associated with volatile anesthetic agent administration, high dose of opioids administered before the onset of surgery and, in certain cases, by the appropriate use of epidural or spinal anesthesia with or without general anesthesia.

Cross-clamping of the thoracic or abdominal aorta to facilitate thoracic or abdominal aortic aneurysm resection or during corrective procedures for aorto-iliac occlusive disease may be associated with significant hemodynamic consequences. The hemodynamic consequences of aortic cross-clamping are influenced by the preoperative coronary circulation and myocardial function, the site of cross-clamp application, the intravascular volume, the anesthetic technique and agents employed, and the surgical pathology. The anticipated consequence of an abrupt aortic cross-clamp will include increased impedance to ventricular ejection (afterload), decreased venous return (preload), with decreased velocity and shortening of myocardial muscle fibers. The hemodynamic consequences of aortic cross-clamping have been extensively evaluated in experimental and clinical studies. Clinical reports consistently demonstrated a 15–30% reduction in stroke volume and cardiac index, coupled with an increase in arterial pressure and up to 40% increase in systemic vascular resistance (17).

Postoperative period

Postoperative blood pressure lability frequently occurs following carotid endarterectomy and may be associated with an increased incidence of neurological complications. Preoperative hypertension, altered baroreceptor activity and abnormal plasma volume have all been suggested as contributing factors. In a study of 166 cases of unilateral carotid endarterectomy, the pre-existence of inadequately controlled hypertension was associated with an increased frequency of transient and permanent neurological deficits (18).

Hypertension is a common and potentially serious complication in the immediate postoperative period following abdominal aortic surgery. Postulated mechanisms include: overzealous hydration during anesthesia and excessive replacement of blood loss; postoperative hypothermia with compensatory vasoconstriction; rebound hypertension following vasodilator therapy; pre-existing hypertension and vascular hyper-reactivity (19). Conflicting findings have been reported by different groups studying plasma renin activity during experimental and human aortic vascular surgery. Depending on the extent of intraoperative hydration, plasma renin activity may increase (20) or remain unchanged (21) following aortic cross-
clamping. A consistent feature of recent studies is the lack of correlation between postoperative hypertension and plasma renin activity or angiotensin II levels in the recovery room (20).

There is a strong association between elevated preoperative arterial pressure and postoperative hypertension (22). Adequate preoperative antihypertensive therapy may be the most important prophylaxis against postoperative hypertension, with its attendant risks of myocardial ischemia and infarction. An acute hypertensive response may be observed in the recovery room due to pain, apprehension, volume overload, hypoxemia or hypercapnia. Management of postoperative hypertension involves exclusion of the underlying cause and prompt initiation of antihypertensive therapy.

III. MANIPULATIONS OF BLOOD PRESSURE DURING ANESTHESIA AND SURGERY

Deliberate hypotension

Deliberate or induced hypotension was introduced in the 1950s to produce optimal operating conditions during certain plastic and neurosurgical procedures and subsequently to decrease intraoperative blood loss and reduced blood transfusion requirements (23). Pharmacological agents, patient position and ventilatory techniques designed to electively reduce blood loss are employed in 3 types of surgical procedures (24). The first is reduction of excessive bleeding during major surgery, e.g. total hip arthroplasty or complicated spinal scoliosis surgery, hepatobiliary, pancreatic or colorectal surgery, and total cystectomy when moderate deliberate hypotension using intermittent positive pressure ventilation and volatile anesthetic agents is usually sufficient. Deliberate hypotension may be used in this manner for patients whose religious beliefs preclude blood transfusion (25). The second is when a dry surgical field is required, e.g. during cosmetic, reconstructive, middle ear or maxillofacial surgery. In these situations, the requirements of moderate deliberate hypotension is associated with gradual onset and slow recovery is best achieved by appropriate patient positioning, volatile anesthetic agents and localized epinephrine infiltration. The third area is vascular and neurosurgical procedures, e.g. cerebral aneurysm clipping, arteriovenous malformation repair, aortic co-arctation repair when profound deliberate hypotension over a relatively short period will be required. In such cases, powerful direct active vasodilators, such as sodium nitroprusside or nitroglycerin may be required in addition to varying concentrations of inspired volatile anesthetic agents.

Techniques to achieve hypotension or hypertension

The methods and drugs used to achieve deliberate hypotension depend on the patient's pre-existing cardiovascular status, the nature of the surgical procedure and their requirements for blood pressure manipulation. High inspired concentrations of volatile anaesthetic agents decrease mean arterial pressure. Halothane is an unsuitable agent for use in deliberate hypotension because, in addition to producing
a dose-dependent decrease in arterial pressure, cardiac output and stroke volume also decrease in a dose-dependent fashion. With the introduction of isoflurane, which lowers arterial pressure by reducing systemic vascular resistance, deliberate hypotension could be induced with little or no change in cardiac output. Maintenance of normal or elevated cardiac output is of central importance to patient safety during induced hypotension. A wide range of intravenous agents has been and can be used to achieve intraoperative deliberate hypotension (26).

Patients undergoing carotid endarterectomy are extremely dependent on collateral flow across the circle of Willis, particularly during carotid cross-clamp. During surgery systemic blood pressure should be maintained at or slightly above the patients’ upper normal limit, with vasopressors if necessary (27). In this setting, most clinicians prefer to use an $\alpha$- and $\beta$-adrenoceptor agonist such as ephedrine or an essentially pure $\alpha$-adrenoceptor agonist such as phentolamine to produce a moderate induced hypertension.

IV. BLOOD PRESSURE MONITORING TECHNIQUES

From this background it will be apparent that arterial blood pressure monitoring has a central role in cardiovascular monitoring during anesthesia and surgery. The decision to utilize direct or indirect blood pressure monitoring technique during anesthesia will depend on a patient’s preoperative cardiorespiratory status, the nature and complexity of the planned surgical procedure, the circulatory volume status and the prospect of sudden blood loss or marked shifts of body fluids during surgery. Indirect measurements will usually be sufficient for the hemodynamically stable patient, without serious cardiac or respiratory disease, who is not expected to undergo marked cardiovascular instability during anesthesia and surgery (28).

Indirect measurement — the sphygmomanometer

With the exception of the recently introduced Finapres, all indirect methods of blood pressure measurement depend on the use of a sphygmomanometer, which measures the pressure required to occlude a major upper or lower extremity artery. A pneumatic bladder enclosed in a cuff is positioned over the artery involved and is inflated to a pressure greater than systolic blood pressure. The air in the bladder is slowly released and one of 4 basic techniques is used to measure systolic and, in some cases, mean and diastolic pressures: auscultation of Korotkov sounds; oscillation of the cuff pressure (oscillometers); differential pressures between sensing and occluding cuffs (oscillotonometers); and detection of blood flow distal to the sphygmomanometer cuff by palpation or Doppler ultrasound (Table 1).

Auscultation of Korotkov sounds

Auscultation of Korotkov sounds is the most basic blood pressure monitoring technique utilized during anesthesia. The extremity concerned is encircled with a Riva-Rocci (air-filled cuff) sphygmomanometer. A pressure greater than systolic is used to inflate the cuff, which distributes the pressure to an underlying cylinder of
TABLE 1. Blood pressure measurement and monitoring in anesthesia

Direct (invasive)

Indirect (non-invasive)
- Auscultation of Korotkov sounds
- Oscillometers
- Oscillogonometers
- Blood flow detection
   - Palpation
   - Doppler ultrasound
   - Plethysmography

...tissue and collapses the brachial artery. A stethoscope is placed over the artery and the cuff is slowly deflated. As systolic pressure is reached, turbulent flow begins through the compressed vessel. This turbulent flow is the source of the bruits known as Korotkov sounds. When the cuff pressures is just below the diastolic pressure, the artery remains patent continually and the Korotkov sounds become muffled.

Auscultation of Korotkov sounds underestimates systolic pressure at high arterial pressures and underestimates diastolic pressure at low arterial pressures. The 95% confidence limits for a single measurement of systolic and diastolic pressures are ± 16 mmHg, and ± 22 mmHg respectively (29). Auscultation of Korotkov sounds may be inaccurate in cases of low cardiac output states or severe peripheral vasoconstriction and when the cuff width is inappropriate for the size of the extremity.

Oscillometers

Oscillometric blood pressure monitoring techniques are based on the detection of arterial pulsations transmitted back to the occluding cuff. The Dinamap blood pressure monitor (an acronym derived from Device for Indirect Non-invasive Automatic Mean Arterial Pressure) was introduced in the mid-1970s (30). The components of this monitor are a microprocessor which controls the entire inflation and deflation sequence and interprets the pressure signals, an air pump to inflate the cuff, a bleed valve to deflate the cuff in discrete decrements of pressure, the pressure transducer and an over-pressure switch to limit the maximum pressure in the system to 300 mmHg. The cuff is inflated through one tube from the pump and the pressure fluctuations in the cuff are sensed through the other tube which leads to the pressure transducer inside the Dinamap. The cuff is initially inflated automatically to 160 mmHg. With subsequent readings the cuff pressure is pumped to a value approximately 35 mmHg higher than the previously recorded systolic pressure and the cuff then deflates in steps of approximately 3 – 6 mmHg, its pressure being momentarily displayed on the mean arterial read-out. The resultant cuff pressure fluctuations recorded by the pressure transducer are then fed into the microprocessor which performs the required logic decisions, rejects artefacts, controls the deflation rate and ultimately displays the reading.
These devices are now widely used in anesthetic practice. They are extremely convenient and generate easily read digital displays. They are accurate and are capable of measuring mean arterial pressure — an important reading in anesthetic practice. They can update their readings frequently and are routinely used to measure pressure every 2–3 minutes during anesthesia. In 'stat mode' the Dinamap can update its reading several times per minute. This is useful in critical situations although it still falls short of the ideal of real time monitoring. Values for 95% confidence limits for the systolic and diastolic pressures of ± 16.4 and ± 15.3 mmHg respectively have been reported. Oscillometry techniques are unsuitable for use in profoundly hypotensive patients.

**Oscillotonometers**

Oscillotonometers were sometimes used for blood pressure monitoring in the pre-microprocessor era. The technique is similar to that described above except that the sensing cuff is separate from the occluding cuff (31). Fairly accurate values for systolic measurements have been reported, but the technique is unsuitable for the measurement of diastolic pressures.

**Blood flow detection**

Techniques for the detection of blood flow distal to the sphygmomanometer cuff include palpation of the pulse and Doppler ultrasound. Systolic pressure may be determined by palpation. The Doppler principle may be used to determine intravascular blood flow (1). Blood in motion in the artery is the target for a narrow ultrasonic beam with a frequency range of 1–10 mHz. Doppler detection of blood flow is especially useful in pediatric and neonatal anesthesia (2).

**Indirect measurement — the Finapres**

The Finapres is a recently introduced device. A small cuff is placed around the finger. This cuff contains an inflatable air bladder, a light source and a photoplethysmographic volume transducer. When blood pressure increases, the walls of the arteries in the finger expand, thus slightly increasing the volume of the finger. This is detected by the photoplethysmograph which signals the central processor. The air bladder is then inflated to oppose the volume change. There is thus a feedback loop in volume to the plethysmograph, the central processing unit and the air bladder. The pressure in the bladder required to oppose finger volume changes closely mirrors blood pressure and thus enables its measurement.

At the time of writing, the role of the Finapres in anesthetic practice has yet to be established. However, it has some very promising features. It appears to be accurate and works well in obese subjects. It is also very convenient. Most importantly, for the first time it allows real-time monitoring of arterial pressure non-invasively.
Direct measurement

Direct measurement of arterial blood pressure and pulse wave analysis supply information concerning the complex interaction between blood flow and the hydraulic impedance to flow in the particular artery. In addition, arterial cannulation facilitates the collection of arterial blood for gas, acid–base and electrolyte determination. Direct arterial pressure monitoring provides the anesthetist with a convenient, continuous, beat-to-beat measurement of systolic, diastolic and mean blood pressure and facilitates the earliest possible recognition of adverse hemodynamic responses to surgical interventions or drug effects.

Principles

Direct invasive arterial pressure monitoring requires an intra-arterial catheter, tubing connecting the monitoring catheter to the transducer, a transducer and a physiological monitor which amplifies, filters and processes the transduced signal and displays the arterial pressure wave form and the derived digital display of systolic and diastolic pressures (32).

The radial artery is usually chosen by anesthetists for direct arterial pressure monitoring because of the accessibility of the wrist, the ease of percutaneous cannulation, the simple stabilization required and the safety implicit in collateral flow through the volar arch anastomosis between the radial and ulnar arteries. Impedance to flow increases from the center to the periphery of the arterial system. Thus, pressure measured in the dorsalis pedis artery will be higher than the radial, which, in turn, will be higher than the brachial artery. Analysis of the arterial pressure wave form from a central artery, e.g. the aortic arch, provides important information concerning cardiovascular function (Table 2). The upstroke of the pulse pressure wave is dependent on left ventricular dP/dt. A steep upstroke indicates strong left ventricular ejection. The area under the systolic ejection phase of the pulse pressure tracing is proportional to the stroke volume and the dicrotic pressure decay is proportional to the systemic vascular resistance.

Technical considerations

The arterial pressure pulse can be considered like a very low frequency sound wave. Frequency is measured in hertz (cycles per second) and at normal heart rate the base frequency of the pressure wave is approximately 1 hertz. In addition there are higher frequencies of harmonics superimposed on this base frequency. However, in neonates or in adults with tachycardias, heart rates up to 240 minutes (4 Hz) may be encountered.

High-fidelity reproduction of an arterial wave form demands reproduction of frequencies up to 10 times the base frequency. Thus, a catheter/transducer system capable of accurately measuring blood pressure must be able to respond to frequencies in the range 0–40 hertz without amplitude or phase distortion. There are two ways to tackle this problem. The ideal would be to design a system whose natural resource frequency was so high that it would be linear from 0–40 hertz without damping. The alternative is to use a system with a resonant frequency closer to 40
TABLE 2. Potential information derived from analysis of arterial pressure recording

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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<tbody>
<tr>
<td>Blood pressure</td>
<td>Systolic/diastolic/mean</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>Upstroke of pulse pressure wave dP/dt</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>Area under the systolic ejection component of pulse pressure tracing</td>
</tr>
<tr>
<td>System vascular resistance</td>
<td>Diastolic run-off below dicrotic notch</td>
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</table>

hertz and to employ optimal damping so as to minimize distortion throughout the vital 0–40 hertz range.

In practice, there is little difficulty designing transducers with high resonant frequencies, but the tubing joining the arterial catheter to the transducer lowers the system resonance frequency close to the vital 0–40 hertz range. In reality, therefore, catheter transducer systems require optimal damping to work properly. It is essential that the tubing used to join the catheter to transducer has the required properties. Very short, wide and rigid tubing may result in an underdamped system which over-reads systolic and under-reads diastolic pressure. Conversely, overdamping due to long floppy tubing or air bubbles may have the opposite effects. In the near future, 20-gauge arterial catheters with optical defocussing pressure transducers built into them will be introduced and should eliminate all the above problems since the system undamped resource frequency will greatly exceed 40 hertz.

The physiological monitor amplifies, filters and processes the transducer signal and displays the pressure wave form. All current physiological monitors also display in digital form the systolic, mean and diastolic pressure.

Contraindications

The radial artery is the most frequently used site for intraoperative direct arterial pressure monitoring. Contraindications to the use of a particular radial artery include circulatory insufficiency in the hand and fingers concerned, the presence of infection in close proximity to the cannulation site and recent cannulation of the same radial artery or the brachial artery above it. The value of the Allen test in determining the presence of adequate collateral circulation through the ulnar artery has been questioned (33). It is now apparent that, in the absence of peripheral vascular disease, the Allen test may fail to predict the presence or absence of ischemic complications. An atraumatic catheter insertion technique, use of smaller 20-gauge short Teflon catheters and prompt removal as soon as clinical circumstances warrant are all important factors in minimizing complications. The catheter should be removed if the hand becomes ischemic, the wave form becomes damped, or blood aspiration becomes difficult.
TABLE 3. *Indications for direct arterial pressure monitoring in surgical patients*

<table>
<thead>
<tr>
<th>Preoperative status</th>
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<tr>
<td>Significant cardiovascular or hemodynamic instability</td>
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<tr>
<th>Specific surgical procedures</th>
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<tbody>
<tr>
<td>Cardiac surgery: cardiopulmonary bypass</td>
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<tr>
<td>Major vascular surgery: carotid, aorta, iliac, vena cava</td>
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<tr>
<td>Intracranial surgery: neoplasms, AVM, SAH</td>
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<tr>
<td>Thoracic surgery</td>
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<tr>
<td>Deliberate hypotension</td>
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<td>Extensive surgery: major blood and extracellular fluid loss</td>
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<table>
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<th>Major trauma</th>
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<th>Technical difficulties</th>
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<td>Obesity, burns</td>
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<th>Arterial blood gas analysis</th>
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<td>Acid – base, electrolytes, glucose hematocrit, coagulation</td>
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AVM = arteriovenous malformation; SAH = subarachnoid hemorrhage.

*Indications for direct arterial pressure monitoring in surgical patients*

The decision to insert an intra-arterial catheter for direct arterial pressure monitoring in surgical patients is based on an assessment of the risk/benefit ratio (Table 3). Arterial cannulation, although an invasive technique, can be readily justified by its high yield of potentially important hemodynamic information with minimum discomfort and, given due care, with low risk.

Direct arterial pressure monitoring is indicated if the preoperative evaluation of the patient indicates significant cardiovascular or hemodynamic instability. In addition, direct arterial pressure monitoring is almost mandatory in certain specific surgical procedures: e.g., cardiac surgery, especially if cardiopulmonary bypass is being utilized; major vascular surgery involving the carotid, aorta, iliac or distal arterial vessels and the vena cava; intracranial surgery including craniotomies for neoplasms, arterio-venous malformation and clipping of ruptured intracranial aneurysms; thoracic surgery, especially when one-lung ventilation technique is employed; deliberate hypotension; and extensive surgery when major blood loss and extracellular fluid loss are anticipated. Direct arterial pressure monitoring is indicated in patients with major trauma, especially when significant hemorrhage has occurred. Obesity and burns on the extremities may make indirect blood pressure recordings difficult and may necessitate direct intra-arterial monitoring. In addition, direct arterial pressure monitoring may be indicated in situations where frequent arterial blood gas determinations will be performed during surgery or when repeated blood sampling for acid–base balance, serum electrolytes, glucose hematocrit or coagulation studies will be performed.
Complications

A number of side-effects and complications have been reported following arterial cannulation for direct blood pressure monitoring (34). These include pain at the cannulation site, local hematoma formation following attempted cannulation, disconnection, hemorrhage, bacteremia and sepsis, embolization, vascular thrombosis and occlusion of the artery with ischemic sequelae. Most of the complications reported following direct arterial pressure monitoring concerned the radial artery. Peripheral embolization of clot and vessel wall plaque to the fingers is usually of little consequence. However, retrograde embolization of air and clot into the cerebral or coronary circulation has been reported to cause disability and death. Such air embolization may occur during manual syringe flushing or prolonged activation of the continuous flow device. The most common and potentially serious complication of radial artery cannulation involves occlusion of the artery with ischemic damage to the fingers or hand. Short-term radial artery occlusion has been reported in up to 25% of patients subjected to radial artery cannulation. However, the incidence of late ischemic damage is very rare. In a series of over 1600 patients, Slogoff and colleagues (33) reported a 25% incidence of occlusion, but no patient developed long-term ischemic injury. Evidence implicating catheter size, catheter type, cannulation technique, and duration of cannulation is ambiguous. Studies have demonstrated a higher frequency of radial artery occlusion in patients subjected to multiple arterial punctures. Investigators have shown a relationship between the incidence of thrombosis and the duration of arterial cannulation (35). However, other studies have failed to confirm this observation (36). Radial artery occlusion was reported to be minimized by using 20-gauge Teflon catheters compared with larger-gauged polypropylene catheters (37). Other studies have found that neither the size nor material of the cannula was related to the incidence of occlusion (40). No case-reports of ischemic damage have been recorded in any prospective study on radial artery cannulation to date. Nonetheless, individual cases have been reported. In the majority of these cases, contributing factors included systemic embolization, prolonged low cardiac output states, vascular disease of the forearm or excessive trauma from surgical cut-downs. The role of the preoperative Allen test in predicting ischemic complications remains controversial. Based on the evidence to date, the Allen test does not appear to be a valid predictor of ischemic injury after radial artery cannulation. Slogoff and colleagues (33) cannulated the radial artery in 16 patients with an abnormal Allen test and no patient developed postoperative ischemic complications. Conversely, Mangano and Hickey (38) have reported a case of ischemic injury requiring digital amputation in the patient with a normal Allen test.

Measurement accuracy

Provided the system is properly calibrated, the displayed waveform has the correct morphology and an appropriate artery is used, the accuracy of direct intra-arterial measurement of blood pressure is assured. Because of this, direct measurement of blood pressure is used as the standard when assessing other non-invasive systems.

Automatic oscillotonometers are widely used in anesthetic practice. They are very convenient and generally more accurate than the auscultatory Korotkov method.
(39). Compared with the direct method, they tend to underestimate systolic and overestimate diastolic pressure while being most accurate when measuring mean pressure (40). In assessing the accuracy of these devices, it is important to consider not only the correlation of a series of measurements with the standard method but also the probability of any single measurement being accurate. In this respect, it is important to emphasize that the oscillotonometric method is most consistently accurate when measuring mean arterial pressure (39). In general, the automatic oscillotonometer is sufficiently accurate to justify its routine use in anesthetic practice in relatively stable situations (41, 42). However, in more critical situations such as transport of critically ill patients (43, 44) deliberate induced hypotension (45) and periods of hemodynamic instability such as occur immediately before and after cardiopulmonary bypass (39), and during severe arrhythmias (41) there is not as yet any substitute for direct intra-arterial measurement.

Other non-invasive methods, such as the use of Korotkov sounds detected with a microphone (41) or stethoscope are less satisfactory and tend to result in more serious underestimation of systolic and overestimation of diastolic pressures while being incapable of measuring mean pressure directly. These methods produce useful trend information but are not sufficiently accurate for use in critical situations.

The Finapres and other prototype devices based on the Peñáz method have only been made available recently and have therefore been less widely assessed than the automatic oscillotonometers. In common with the direct method, this method has the important advantage of providing real-time information. These devices have been studied in a variety of situations. Early reports differ somewhat concerning the devices' accuracy when measuring mean and diastolic pressures. Some studies found them to be accurate (47) measuring mean pressure compared to the direct method, others have found them to underestimate mean and diastolic pressure (48, 49) while they have been reported to overestimate mean and diastolic pressure during spinal anesthesia (50). However, most studies have reported that they consistently overestimate systolic pressure, especially during exercise and spinal anesthesia. This method requires further evaluation before its role in anesthetic practice is defined.

V. SUMMARY AND CONCLUSIONS

Automated, non-invasive monitoring of blood pressure, especially using the oscillometric method, has a major role in anesthetic practice for routine surgery in relatively fit patients. It is rapidly displacing the less accurate and less convenient manual non-invasive methods. However, direct measurement of blood pressure remains more accurate and reliable and this accuracy together with its ability to convey data continuously and in real time assures its continued pre-eminence in the anesthetic management of more critically ill patients and patients undergoing major surgery.

REFERENCES


18. Measuring blood pressure in laboratory animals

Ruben D. Buñag

Reliable blood pressure measurement is as indispensable now as when interest in hypertension research first began, yet the need for accurate measurement is often ignored. Although an unequivocal diagnosis of hypertension can be made only if blood pressure can be measured accurately, the methods used for measurement are usually taken for granted, considered negligible, and often described superficially if at all. Contrary to this lackadaisical attitude, however, when the current state of research was assessed by the Hypertension Task Force established in 1979 by the National Heart, Lung, and Blood Institute, their findings were summarized as follows (1): ‘The methods that are available for the direct or indirect determination of blood pressure in chronic experiments in unanesthetized animals are barely adequate for such studies. The commercial equipment available for this purpose is in many cases unsatisfactory. Improved techniques for blood pressure measurement in long-term experiments would, of course, facilitate research in all aspects of hypertension.’ Based on this and also because further improvements in methodology since 1979 have been meager, the accuracy of repeated blood pressure measurements (i.e. particularly those taken during long-term studies in conscious animals) still remains frequently questionable.

Experimental hypertension, defined as a sustained and long-lasting blood pressure elevation, can be shown to exist only by measuring blood pressure over and over again in the same animals, preferably while they are conscious to avoid artefacts due to anesthesia. In trying to accomplish this, the ease with which blood pressure can be measured repeatedly without using anesthesia varies inversely in different animal species with body size and lifespan. For instance, in rats and dogs, which are the two species most commonly studied in hypertension research, if all other factors that could influence blood pressure measurements were kept constant, then blood pressure can be measured more easily in dogs than in rats simply because dogs are bigger than rats. On the other hand, since hypertension usually progresses rather slowly with time, the ease with which its development can be monitored also varies inversely with the animals’ lifespan such that the development of hypertension can be detected more rapidly in rats which normally live for only 2–3 years than in dogs which have a longer lifespan of 12–20 years. Accordingly, based on
either body size or lifespan alone, the technical difficulties involved in measuring blood pressure during chronic studies on experimental hypertension depend in part on the animal model.

The first recorded attempt to measure blood pressure quantitatively was done by the Reverend Stephen Hales in 1733 (see Chapter 1) on an unanesthetized horse. By connecting a 9-foot long glass tube to a brass pipe inserted into the femoral artery, he allowed arterial blood to flow into the glass tube and ignoring the need for either anesthesia or a manometer, he simply recorded the height to which arterial blood oscillated inside the glass tube. While he was indeed able to measure mean pressure, the crude methods he used would presently no longer be accepted not only because of technical problems caused by clotting or hemorrhage, but more importantly because the pain or stress he willfully inflicted on a conscious horse would nowadays arouse considerable animal care concerns. Inasmuch as the voluminous literature published following Hale’s original report has already been reviewed comprehensively by Geddes in ‘The Direct and Indirect Measurement of Blood Pressure’ (2), most of the papers examined here have been restricted to those published after 1970 and the text organized to highlight direct and indirect methods currently applied for studying experimental hypertension.

Although the general principles for measuring blood pressure are the same regardless of animal species, current research on experimental hypertension is done predominantly in rats and most of the methods reviewed here consequently pertain to blood pressure measurement in this species. Of 4030 articles published in scientific journals from 1985 through 1988 relating to experimental hypertension, 2784 or 69% were on rats and 354 or 9% were on dogs. In trying to explain why rats are frequently chosen instead of other animals for studying hypertension among the reasons cited previously are: their uniformity in body size and genetic background, relatively low costs, and the availability of several models for experimental hypertension (3). Considering the recent resurgence of interest in animal rights, perhaps another reason might be that rats are less likely than dogs or cats to arouse sympathy from animal rights activists.

I. RATS

Many of the methods used for measuring blood pressure in rats are still the same ones that were reviewed in 1983 (4) and 1984 (5), but the information given here has been updated to include recent references.

Blood pressure recording in anesthetized rats

In most animals (including rats) immobilized by anesthesia, blood pressure can be recorded easily even by technicians without previous training or experience. Intraarterial pressures can be recorded continuously by inserting catheters made of small-bore tubing into suitable arteries and then connecting the catheter to a mercury manometer or pressure transducer. The fidelity of such recordings is affected by many factors, especially the characteristics of the transducer and its fluid-filled con-
nection to the rat. Among the usual sites cannulated are the aorta or the carotid, iliac, femoral, or caudal arteries.

Mercury manometers were first introduced for recording blood pressure by Poiseuille in 1928 and have since then been so widely used that blood pressure is now still commonly expressed in conventional units of millimeters of mercury (mmHg). However, because inertia and friction of the mercury column markedly reduce the amplitude of arterial pulsations, mercury manometers should be used to record only mean but neither systolic nor diastolic pressure. In light of this the use of pressures recorded directly with mercury manometers as references to validate indirect measurements obtained with the tail-cuff method (6–8) is inappropriate because the ensuing comparisons are bound to be misleading (i.e. mean pressures registered with a mercury manometer would always be lower than the corresponding systolic pressures detected by tail-cuff measurement) (9). A U-tube manometer registers much smaller pulsations in rats (which have smaller bodies and faster heart rates) than in dogs, not only because heart rate is inversely related to body size but also because the magnitude of arterial oscillations diminishes as the heart rate increases. In the Condon rat manometer (Harvard Bioscience, South Natick, MA) ensuing errors in blood pressure estimation have been corrected by connecting a 2.5-mm bore glass tubing to a 25-mm diameter reservoir so that changes in the mercury level of the reservoir would be magnified 10-fold to display larger changes in the glass tube. By adjusting a screw clamp placed on tubing connections between the manometer and the rat, amplitude of oscillations can be reduced almost completely and mean pressures can then be estimated reliably.

Pulse pressures in rats can be measured precisely only with pressure transducers with a low volume displacement (e.g. Statham P23 Gb with a volume displacement of 0.01 mm³/100 mmHg). As the volume of blood displaced into the recording system is proportional to pulse amplitude, the volume displacement of transducers designed for use in larger animals like dogs (whose pulses would be much stronger than those in rats) may not be low enough to reproduce pulse pressures accurately in rats. Apart from the transducer itself, the fluid-filled tubings that connect the transducer to the rat would also influence fidelity of pressure wave reproduction. Volume displacement increases when elastic or non-rigid tubings (e.g. silastic or thin-walled Tygon which are expandable) are used for catheters, or when air-bubbles (which are compressible) are present anywhere in the system. Small air bubbles may adhere to the tubing connections, walls of the transducer dome, or stopcocks connected to the dome for flushing. Ensuing errors can be minimized by using rigid-walled tubings (e.g. polyethylene or Teflon) to make catheters, or by filling the system with boiled water to which some alcohol or a wetting agent has been added. For authentic reproduction of the blood pressure wave the whole recording system (including the transducer and all its fluid-filled connections) must have a uniform sinusoidal frequency response up to about the 15th harmonic. According to Geddes (2) for good reproduction of the blood pressure wave, the over-all system sine-wave frequency response should extend uniformly from zero to 10 times the heart rate. In order to reproduce the arterial pressure wave well enough to show a distinct dicrotic notch, recording systems used in rats (whose normal heart rates range from 250 to 350 bpm of 4–6/s) should have a uniform frequency response from zero to 60 Hz.
Blood pressure recording in conscious rats

Even when conscious rats are immobile, they can still react to stress and environmental stimuli with considerable cardiovascular effects which could complicate interpretation of blood pressure measurements recorded without anesthesia. Conscious rats can be stressed as they are handled either for connection of indwelling catheters in preparation for direct recording of intra-arterial pressure or for placement in heated restrainers during tail-cuff measurement. Precautions that could reduce stress-induced pressor responses include: training the rats by repeated exposure to the required procedures, discarding results of initial trials until stable values are obtained, and taking all measurements under rigidly controlled environmental conditions (i.e. have measurements taken regularly by the same technician at the same time each day in a sound-insulated room with controlled light and temperature). Once the rats become accustomed to the recording procedure, blood pressures usually remain quite stable from day to day and any sudden deviations from the norm should always be viewed with suspicion as being indicative either of a sudden change in the recording environment or more importantly, of the actual development of hypertension.

Continuous recording of intra-arterial pressure

Indwelling arterial catheters, which are usually used only once during acute experiments on anesthetized rats, can be used repeatedly for recording intra-arterial pressures during chronic experiments in conscious rats. During surgical implantation the outer end of the catheter is usually passed subcutaneously to emerge at the nape of the neck from where it cannot be pulled out easily by the rat. For short-term experiments lasting only a few days, surgical manipulation can be greatly reduced by cannulating the caudal instead of the iliac or femoral arteries; thus, even without opening the abdominal cavity a single short piece of polyethylene tubing can be inserted directly into the caudal artery (10–12).

Unlike acute experiments on anesthetized rats in which the pressure transducer is ideally placed on the same level as the rat's heart, in chronic experiments on conscious free-moving rats the transducer usually has to be placed above the rat's cage. For instance, when a harness-and-swivel arrangement was used for recording cardiovascular responses to injected drugs (13), hypothalamic stimulation (14, 15), or mechanical shaking (16), the transducer was placed, together with the swivel, above the rat cage. The hydrostatic pressure thereby created adds about 1 mmHg of extra pressure for every 1.36 cm in vertical distance between the transducer and the rat's heart. To record the actual arterial pressure level, a correction factor obtained by dividing height of the fluid column by the ratio between the densities of mercury and water can be added during calibration of the transducer. Alternatively, the transducer can be calibrated while it is open to a fluid-filled catheter placed at heart level.

Stagnation, caused by interruption of blood flow following arterial cannulation, enhances the formation of clots and fibrous outgrowths which may clog up the catheter. Clot formation can be reduced by filling the arterial catheter with dilute heparin solution (200 U/ml), but occlusive plugs due to vascular wall fibrosis could
still be formed. Isotonic saline from a pressurized reservoir can be infused slowly into the arterial catheter to keep it open and thereby allow uninterrupted recording for several hours (17). Nonetheless, emboli released from carotid catheters may cause renal infarction while those from iliac or femoral catheters may result in hind-leg paralysis (9). To circumvent problems caused by stagnation, Weeks and Jones devised (18) an ingenious cannulation procedure whereby the catheter, instead of being tied into the femoral or iliac artery, is inserted directly through the wall of the lower abdominal aorta without blocking the flow of blood. They used heat-welded pieces of PE-10 and PE-20 polyethylene tubing to make an arterial cannula containing a loop on the PE-10 portion to serve as a shock absorber for damping vibrations of the cannula tip inside the aorta. This method has subsequently been used together with a rotary switch, to allow sequential measurements from several rats through a single transducer, and a computer for data analysis (17). Indwelling aortic catheters have been used to monitor mean arterial pressures in conscious rats continuously for several hours following sino-aortic denervation (19, 20).

Many of the technical difficulties caused by indwelling catheters can be avoided by using radio-telemetry. A new system (Data Sciences Inc., St. Paul, MN) consisting of an implantable strain gauge transducer-transmitter has recently been described for continuous blood pressure measurement during chronic studies in conscious rats (21). Implanted into the peritoneal cavity, the miniaturized transducer-transmitter is connected to an aortic catheter (coated with an antithrombogenic film to minimize blood clots and its tip sealed with a viscous gel to prevent blood from entering the catheter), and pressure signals from the transmitter are then detected by an accompanying receiver, placed within the recording vicinity, for computer processing. In validation studies done on anesthetized rats 3–12 weeks after transmitter implantation, systolic and diastolic pressures registered with this system approximated within ± 5 mmHg those recorded simultaneously from the left carotid artery in 78–86% of the rats tested. If a similar degree of accuracy can be attained over several months even in conscious free-moving rats, then this system, though almost prohibitively expensive (i.e. initial costs estimated now at about $12,000 for every 6 rats), would eliminate most of the stresses presently associated with indirect measurements.

Indirect measurement using occlusive cuffs

Direct recording of intra-arterial pressure from an indwelling catheter, though undoubtedly much more accurate than any indirect measurement, has the disadvantages of requiring surgery, anticoagulants, and possibly producing hemodynamic alterations (22). For long-term studies like those involving progressive blood pressure changes produced by dietary manipulation or aging, the greatest limitation of direct recording is that arterial pressures cannot be measured accurately from indwelling catheters for more than a few weeks. Even with skilled technicians using the Weeks and Jones (18) cannulation procedure, mean arterial pressures can be recorded for only 6 weeks. By contrast, indirect measurements do not have any of the above-mentioned disadvantages and they can be repeated for as long as the rats live if necessary. Consequently, the method of choice for measuring blood pressure
during chronic studies on conscious rats has been an indirect method applied to either a hind-leg or the tail.

By using the rat’s hind-leg for indirect measurement, systolic pressure can be measured even without preheating the rat to induce vasodilation. In rats trained to stand slightly crouched on both hind-legs in a special holder, Kersten and colleagues (23) used a photocell-ammeter to register volume changes occurring in the foot during cuff deflation. Systolic pressure, indicated by a fall in the ammeter reading, corresponded closely with that obtained by femoral puncture in anesthetized rats (24), but the end-point was imprecise, easily obscured by movement artefacts, and highly prone to subjective operator errors. In later studies when Olmsted and colleagues (25) compared systolic pressures recorded from either the foot or the tail, they found a close correlation between the values obtained with the two indirect methods. Despite these early studies, however, the foot method never became popular (probably because it is difficult to train rats to stand on their hind-legs) and the required equipment is no longer commercially available. Aside from anatomical differences between the foot and the tail, vascular reactivity in the two sites may be very different, because as rats use their tails for regulating body heat, the tail vessels are more apt to respond to stimuli that increase sympathetic vasomotor tone to induce localized vasoconstriction.

As stated somewhat wryly in a previous review (4), ‘a rat’s tail is a slender appendage on which the weight of so much research in hypertension hangs’. That statement was based on the fact that as a result of its widespread use during the last 3 decades, the tail-cuff method accounts for much of the information now available on blood pressure in hypertensive rats. Being non-invasive and relatively easy to use, the tail-cuff method was generally believed to be so ‘simple’ — as originally described by Williams and colleagues (26) in 1939 and later repeated by Gallagher and Grimwood (27) in 1953 and by Alexander (28) in 1957 — that it could be used to measure blood pressure, easily and with unerring accuracy, in unanesthetized rats even under widely varying laboratory conditions. Yet while the method is indeed easy to use, its apparent simplicity can be deceptive because the naive assumptions that are usually made about its accuracy often remain unsubstantiated.

Factors affecting reliability of tail-cuff measurement With any indirect method the accuracy with which blood pressure can be measured is greatly influenced by the length of the artery that is compressed which in turn depends on a balance between width of the occluding cuff and the diameter of the extremity on which the cuff is applied (2). In principle, an annular occluding cuff applied to the base of the rat’s tail is inflated to interrupt blood flow and upon slowly deflating the cuff, systolic pressure is determined as the cuff pressure at which a pulse (signifying resumption of blood flow) can be detected distal to the point of occlusion. When cuffs of the same size are applied to extremities with different diameters, the length of the arterial segment compressed becomes inversely related to the diameter of the extremity (i.e. arterial length decreases as extremity diameter increases and vice-versa). Thus, Maistrello and Matscher (29) found that the tail segments compressed by a 16-mm cuff in rats weighing 100–300 g were significantly longer than those in bigger rats weighing 300–500 g (average lengths of the tail segments compressed were 13.86 and 10.89 mm respectively, \( P < 0.001 \)). Despite repeated attempts to establish
optimum cuff width, however, there is no universal agreement because the best cuff width may vary depending on the amount of vascular tone present at the time of measurement. Sobin (30) showed that indirect measurements taken with 10 or 40 mm cuffs were markedly improved after local vasodilation was induced by warming the tail. The most accurate estimations of systolic pressure in anesthetized rats have been obtained with cuffs ranging in width from as small as 5 mm (31) to as much as 37.5 mm (32). It now appears improbable that any single cuff width would work well under all conditions because optimal cuff length may vary with the recording system used. In conscious and preheated rats, the best agreement between tail-cuff and simultaneously recorded intra-arterial systolic pressures has been obtained with 15-mm cuffs (33, 34).

Vasoconstriction in the rat's tail often becomes troublesome during tail-cuff measurements because arterial pulsations cannot be detected in constricted vessels even with the most sensitive sensors now available. Rats regulate their body temperature primarily by changing blood flow in their tails (35) so that the tail vasculature reacts strongly to most stimuli. Because of this, any deviation from normal routine during tail-cuff measurements can cause the tail vessels to constrict and render detection of end-point pulsations difficult, if not altogether impossible. Barely audible noises lasting for just 1 second can consistently provoke vasoconstriction in the tail vessels (36). In many tail-cuff methods, preheating has been used to dilate the tail vessels and thereby counteract stress-induced vasoconstriction, but as the amount of preheating required varies from one rat to another, it is difficult to standardize (23). Furthermore, since adequate vasodilation occurs only after rectal temperature has been elevated by 0.8°C (31), the amount of preheating applied can have significant pressor effects (37–39) that would make basal blood pressure levels erroneously high. Early studies on unanesthetized rats exposed to radiant heat for 10 minutes showed that when rectal temperatures were increased by 0.4–2.0°C, tail-cuff systolic pressures could be elevated by as much as 80 mmHg (37). Smaller pressor effects occurred in conscious rats exposed to a heat lamp for 15–20 minutes while aortic blood pressure was being recorded continuously; increases in rectal temperature of 0.5–1.5°C were accompanied by mean pressure elevations of 5–20 mmHg (39). In both these studies, however, heating may not have been solely responsible since restraint and other stresses during measurement may have contributed to the resulting pressor effects. Heat-induced errors can be minimized by applying just enough heat to increase pulse volume to 25% of the maximum obtainable (40), but other errors can still occur, particularly in rats with varying susceptibilities to thermal stress. For instance, since spontaneously hypertensive rats (SHR) are more susceptible to heat than Kyoto-Wistar normotensive ones (41), part of the higher pressure values obtained in SHR with tail-cuff methods that require preheating may reflect heat-induced pressor effects rather than actual hypertension. Obviously, such problems can be avoided by using methods that do not require preheating.

Another important determinant of accuracy in tail-cuff measurements is the sensor used for end-point detection. Earlier equipment using water-filled plethysmographs, optical pressure transducers, oscillometric pulse detector cuffs, and carbon microphones have already been reviewed by Geddes (2). Since then validation studies have been published on the following: strain-gage plethysmograph (29),
pulse transducer (34), Doppler ultrasonic flowmeter (33, 42), photoelectric sensor
(43, 44), plethysmographic chamber (45), servo-control system with a photoelectric
plethysmograph (46), light-emitting and photo-diodes (47, 48), and differentiated
impedance (49). In general, the sensor has to be sufficiently sensitive to detect the
first arterial pulsation that appears as the occluding cuff is gradually deflated, and
most of the newer sensors (i.e. the last 3 listed above) are claimed to be capable of
pulse detection in conscious rats even without preheating.

With most tail-cuff methods, unanesthetized rats have to be restrained and
preheated during measurements and since restraint and heat can elicit substantial
pressor effects, the existence or severity of experimental hypertension can become
falsely exaggerated. Thus, the incidence of hypertension after unilateral clipping of
the left renal artery was 25% higher when tail-cuff pressures were measured with
preheating than when intra-aortic pressures were recorded from the same rats
without preheating (39). Significant pressor responses caused by restraint during
tail-cuff measurements have been reported in spontaneously hypertensive rats (10).
Similarly, Norman and colleagues (19) found that pressures within the hypertensive
range were obtained following sino-aortic denervation only when tail-cuff
measurements were made intermittently while the rats were restrained in heated
holders, but not when intra-aortic pressures were recorded continuously while the
same rats were not heated and kept in metabolic cages instead of being restrained.
Such errors could in part explain why mild hypertension in rats with streptozotocin-
induced diabetes has been detected only by tail-cuff measurement, but not upon
direct recording from indwelling arterial catheters (50, 51). In this particular
instance instead of producing hypertension, streptozotocin treatment may have in-
creased sensitivity to stress sufficiently to enhance pressor responses occurring dur-
ing tail-cuff measurement.

Proper validation of tail-cuff methods to be used in conscious rats Although it
seems blatantly obvious that methods intended for use in conscious rats should be
tested for reliability also in conscious rats, tail-cuff methods are often validated in
anesthetized rats (7, 27, 29-32, 37, 48, 52-57) instead. This common but ques-
tionable practice incorrectly assumes that as anesthesia does not affect blood
pressure, any methods proven to be sound in anesthetized rats must perform remain
equally reliable even after the rats regain consciousness. Contradicting this assump-
tion, it can be argued that as anesthetics depress brain and baroreceptor mechanisms
that regulate blood pressure, what is being measured while the rats are anesthetized
must have been altered unavoidably by anesthesia. Moreover, studies designed to
assess tail-cuff measurements by comparing them with simultaneously recorded aor-
tic pressures have shown that even when both measurements correlated well while
the rats were anesthetized with ether, the correlations became worse when simultane-
ous measurements were repeated while the same rats were conscious (9). Despite the
increases in circulating catecholamines during ether anesthesia, based on a
rather unusual validation in which tail-cuff measurements from ether-anesthetized
rats were compared with systolic pressures recorded separately from carotid
catheters in conscious rats, ether anesthesia has also been claimed to be devoid of
effects on tail-cuff systolic pressures (57).

Simultaneous recording in conscious rats of tail-cuff and intra-arterial pressures
was reported in 1971 originally by Buñag and colleagues (9), then by Patten and Engen (58), and later by Pfieffer and colleagues (34). Correlations obtained from ensuing comparisons of simultaneously recorded direct and indirect measurements were poor in the first two studies but good in the third. Inasmuch as simultaneous recordings can be taken only by restraining preheated rats (i.e. to allow application of the tail-cuff method), all the ensuing pressure readings, whether obtained by direct or indirect measurement, would also include pressor responses to stress. Some discrepancies may have been due to differences not only in the reference pressure employed but also in sensor sensitivity. When similar comparisons were repeated using a Doppler ultrasonic flowmeter (which is more sensitive than the pulse transducer studied earlier) for end-point detection, correlations between tail-cuff and carotid systolic pressure were highly significant (33). Recent validations made using photo-electric sensors (44), light-emitting diodes (57), or differentiated impedance (49) have also shown reliable tail-cuff measurements in conscious rats.

Blood pressure values obtained with the tail-cuff method can be influenced by the arterial site from which reference pressures are recorded for comparison. In anesthetized rats validation studies have been almost evenly divided in using either carotid (6, 7, 25, 29, 54-47) or femoral (24, 30, 31, 37, 45) arterial pressure, while in unanesthetized rats, reference pressures have been recorded from the lower abdominal aorta (9), or carotid (33, 34, 44, 47) or femoral (49) arteries. Considering the anatomical proximity of the femoral artery (i.e. it is nearer than the carotid artery) to the tail, Geddes (2) believes that femoral arterial pressure is the appropriate reference for tail-cuff measurement. On the other hand, systolic pressures in the carotid artery or thoracic aorta are bound to be lower than those recorded from the iliac artery or lower abdominal aorta because systolic pressures within the aorta become progressively higher as one gets farther away from the aortic arch. Comparisons with an intra-arterial reference pressure may also be influenced by the location of the sensor on the rat’s tail; since caudal arterial pressures decrease progressively as one moves from the base to the tip of the tail (30, 31), the corresponding pressures that can be recorded indirectly would also become lower as the sensor is placed farther away from the base.

To determine where the best reference pressure can be found, I recorded phasic arterial pressures simultaneously from separate catheters inserted into the caudal, left carotid, and left iliac arteries in anesthetized rats (33). Average diastolic pressures were the same at all 3 sites, but corresponding systolic pressures in the iliac artery (169 ± 13 mmHg) were significantly higher (P < 0.001) than those in either the carotid (159 ± 12 mmHg) or caudal (161 ± 12 mmHg) arteries. Inasmuch as carotid and caudal systolic pressures were almost identical, I then recorded carotid and tail-cuff systolic pressures simultaneously in a mixed group of unanesthetized SHR and normotensive rats. Average systolic pressures of 176.8 ± 26 mmHg from the carotid catheter and 176.7 ± 25 mmHg with the tail-cuff method (correlation coefficient = 0.974; P < 0.001) were obtained. In those early studies the sensor was a Doppler flowmeter, but similar comparisons made later using a photo-electric sensor in unanesthetized normotensive rats also yielded identical average systolic pressures of 137 ± 1 mmHg for both the carotid and tail-cuff measurements (44). From these results it is clear, therefore, that for the two tail-cuff methods tested, carotid arterial pressure was the ideal reference.
Tail-cuff measurements without preheating. Because pressor responses to preheating could falsely elevate pressures obtained by tail-cuff measurement, sensors capable of detecting caudal arterial pulsations even in the absence of heat-induced vasodilation seem preferable and have been described from time to time (29, 55, 59). However, such sensors were usually custom-made and did not become commercially available until 1977 when Yen and colleagues (43) described a new photo-electric sensor which was then manufactured for commercial distribution by IITC Inc (23924 Victory Blvd., Woodland Hills, CA) and later validated in conscious rats by Buñag and Butterfield (44). Since other tail-cuff methods tested previously had either exaggerated or underestimated drug-induced changes in blood pressure (13, 60), we first compared systolic pressures recorded simultaneously in amobarbital-anesthetized rats during intravenous infusions of norepinephrine or sodium nitroprusside. Systolic pressures obtained with both methods were exactly the same and the correlation between them was highly significant (correlation coefficient \( r = 0.939 \)). Subsequent comparison in conscious rats of systolic pressures recorded similarly with the tail-cuff method or from carotid catheters also gave exactly the same average of 137 ± 1 mmHg with a correlation coefficient of 0.962 (slope 1.023, \( y \)-intercept 3.485; \( P < 0.001 \)).

Even though the IITC sensor could detect tail pulsations in rats that had not been preheated, it became unreliable at room temperatures below 27°C probably because the tail vessels normally remain dilated at environmental temperatures between 27 and 30°C (35). In heated rats adequate tail pulsations occur when rectal temperature has been elevated by 0.8°C (31) and comparable increases in rectal temperature can be attained even without preheating by simply confining the rats in a holder for 30 minutes (44). The ensuing vasodilation is not, however, strong enough to overcome stress-induced vasoconstriction, so that whenever the rats are uncomfortable or unfamiliar with surrounding conditions, reliability of tail-cuff measurements with the IITC sensor is reduced because the ensuing stress causes the tail vessels to constrict. By contrast, with methods that employ preheating, by applying heat to keep the vessels dilated, tail pulsations can be detected even during stress-induced vasoconstriction (33), but then artefacts due to stress-induced pressor responses would occur. Hence, even if the more sensitive sensors described recently (47, 49) could enable measurements in the presence of stress-induced vasoconstriction, all tail-cuff measurements should still be made under rigidly controlled environmental conditions.

Using the tail-cuff method to quantify drug effects. Despite frequent use of the tail-cuff method for routine measurement of cardiovascular drug effects, contradictory results have been obtained particularly when the blood pressure changes are modest or small. Equating drug effects obtained in other animals with those detected by tail-cuff measurement in rats (61) may be misleading because most active drugs, aside from altering systemic pressure, also have local effects on the tail vasculature which can modify the pressure levels registered by indirect measurement. Vasoconstriction induced by pressor agents like angiotensin or norepinephrine may become strong enough to obliterate caudal arterial pulsations and thereby prevent end-point detection even with methods that employ preheating. Tail-cuff pressures have been found to be either undetectable or erroneously low following injections or infusions of
epinephrine, norepinephrine, or renin (28, 29, 52). While intra-arterial pressures were not recorded in any of these studies, the weakening of tail pulsations in the presence of vasoconstricting drugs has been confirmed. In unanesthetized rats, systolic pressures measured with the tail-cuff method were frequently lower than those recorded simultaneously from indwelling aortic catheters following injections of norepinephrine (9). Subsequent studies have also shown (60) that whereas pressor responses to small doses of infused norepinephrine or angiotensin could be measured accurately with the tail-cuff method, those exceeding 33 ± 4 mmHg were either underestimated or undetected.

Contradictory results have likewise been reported following administration of hypotensive drugs. Van Proosdij-Hartzema (62) actually recorded paradoxical pressor responses by tail plethysmography (i.e. opposite to the hypotensive responses recorded simultaneously from the carotid artery) following intramuscular injections of drugs customarily considered to be hypotensive like hexamethonium, mecamylamine, phentolamine, or reserpine. These results may, however, have been unique only for the plethysmographic method she used because depressor responses to phentolamine or pentolinium have been obtained in other studies by simultaneous direct and indirect measurements (60).

Differences in regional vascular responses to systemically administered drugs may contribute to the discrepancies between direct and indirect measurements. Upon recording phasic pressures simultaneously from carotid, aortic and caudal arterial catheters, infusions of sodium nitrite, phentolamine, or pentolinium did not lower systolic pressures uniformly at all 3 sites (13). For instance, the lowering in systolic pressure produced by phentolamine was more pronounced in the aorta and caudal artery than in the carotid artery, and if carotid arterial pressures were used as the reference during phentolamine-induced hypotension, then the tail-cuff method would over-estimate the fall in systemic pressure (60). Similar errors in attempts to quantify hypotensive responses to hydralazine, prazosin, and two prostaglandins (PGE₁ and PGE₂) have also been reported following comparison of femoral and tail-cuff systolic pressures (63).

Considering all the possible errors that can be made, one should not rely solely on tail-cuff measurements to monitor drug-induced responses. As a prudent safeguard against such errors, before accepting any blood pressure changes detected by tail-cuff measurement during drug administration in conscious rats, the blood pressure effect should be verified by direct measurement in the same rats.

Present state of the art of tail-cuff measurements As the tail-cuff method still continues to be the method of choice for measuring systolic pressure in chronic studies on hypertensive rats, those interested in using it should be fully aware of its many limitations. For laboratories that have never used the tail-cuff method before, regardless of the sensor selected, its reliability should ideally be established under the same experimental conditions that would exist when it is later used for actual measurements. This means that instead of simply citing publications describing validation studies that were done elsewhere, each laboratory should, whenever possible, do its own validation. Although repeating validation of the same method may seem needlessly time-consuming, common acceptance of validation done by others is bound to be misleading because it dubiously assumes that all laboratories
and technicians are created equally. Quite to the contrary, however, no two laboratories are ever exactly alike and different technicians can mismanage conscious rats during tail-cuff measurements in many different ways.

Selection of an appropriate tail-cuff method depends largely on how the method will eventually be used. If it is to be used solely for separating normotensive from hypertensive rats in populations with established or long-standing hypertension, then the anticipated blood pressure differences between groups will be large and any tail-cuff method, whether validated properly or not, should prove more than adequate. But when it is to be used for detecting the onset or initiation of hypertension, then the blood pressure differences would be more subtle and the tail-cuff method selected must be absolutely accurate and dependable. Equally rigorous requirements should also be applied for tail-cuff methods to be used for monitoring blood pressure responses to chronically-administered vasoactive drugs which could have spurious effects on the caudal vasculature. Regardless of the particular tail-cuff method employed, possible errors can be minimized by routinely doing terminal experiments to record blood pressure directly from indwelling arterial catheters in the same rats. Finally, although tail-cuff equipment linked to computers for data analysis are now commercially available, whether computer programs can be written to compensate for all the possible errors that could occur during tail-cuff measurements in conscious rats still remains uncertain.

II. DOGS

Following the same procedures described for rats, blood pressure can be recorded directly from indwelling arterial catheters in dogs, whether conscious or anesthetized. The method described originally by Herd and Barger (64) for surgical implantation of catheters made of polyvinyl chloride tubing has been widely used together with various valve devices (65–67) that allow chronic exteriorization to the skin. However, the length of the catheter delays recording of the phasic wave and the high inertia of the fluid inside the catheter lowers the frequency response of the recording system (68). With the increased body size in dogs, other methods for direct recording which cannot be applied in rats have been tried. One method involves surgical creation of an external arterial loop by raising a carotid artery, enclosed in a tube of skin, to the surface of the neck where it can be punctured directly with a needle (2, 69). In another method uniquely applied to purebred beagles which have unduly large ears, mean arterial pressure has been recorded for several weeks by repeated puncture of the central ear (i.e. intermediate auricular) artery with a 22-gauge needle (70). Catheter microtip manometers (Millar Instruments, Houston, TX) have also been used in acute experiments but are not recommended for long-term measurements because they do not remain sufficiently stable with time and the relative stiffness of the catheter can produce considerable movement artefacts (68).

Implantable pressure transducers may provide more elegant measurement procedures, but also require more funds and technical expertise than most laboratories can afford. Such transducers measuring 3–7 mm in diameter and constructed using a titanium diaphragm (Konigsberg Instruments, Pasadena, CA) have long been used routinely by Vatner and his associates for chronic studies in various mammals in-
cluding dogs, sheep, and monkeys. Compared with fluid-filled catheter systems, implantable transducers have a better frequency response and are suitable for telemetry (68), but in chronic use have major disadvantage due to drifts in zero offset and sensitivity (71). To eliminate drift as a source of error in long-term studies, implanted transducers need to be calibrated in vivo (i.e. by comparison with reference pressures recorded simultaneously using a calibrated microtip transducer or catheter-manometer system) at least once every 2 weeks (72). By combining implantable transducers with radiotelemetry, connecting cables or tethers are no longer needed and blood pressure can be recorded while the animals are in their natural habitat. In contrast to the portable transmitter (D70 package available from Data Sciences Inc. see page 9) designed for chronic subcutaneous implantation, one for each dog, radiotelemetry systems have been used in a back-pack arrangement which can be shared among a number of dogs, and also calibrated and repaired easily at considerably less expense (71).

Many indirect methods have also been described for repeated blood pressure measurement in chronic studies on conscious dogs. The tail, in contrast to its convenience for indirect measurement in rats, is not as commonly used in dogs because the canine caudal artery is relatively small and pulse detection from it is difficult. Consequently, indirect measurements in dogs are more frequently taken from the leg rather than the tail, but there are technical difficulties present in any measurement site. In the forelimb the brachial artery is also small and the humerus short, while on the hindleg, even though the femoral artery is large and superficial, occluding cuffs cannot be applied easily (2). What can be measured indirectly also differs between the two species: whereas only systolic pressure alone can usually be recorded in rats, both systolic and diastolic pressures have been obtained routinely in dogs.

Despite species differences, the general principles and difficulties of indirect blood pressure measurement in dogs are the same as those that have already been discussed for rats. Indirect measurements in dogs have been taken from the foreleg (73–77, 84), hindleg (78–81, 83) or tail (82) with reference pressures for comparison obtained by arterial puncture (74, 78, 79) or cannulation (73, 75–77, 80–83) from the femoral (73, 75, 77–79, 81–83), tibial (80), or carotid (75–77, 83) arteries. Though intended for use in conscious dogs, indirect methods are still commonly validated (i.e. compared with simultaneous recordings of intra-arterial pressure) in dogs that are either sedated (73, 78, 82) or anesthetized (74–77, 79–81, 83).

III. OTHER ANIMALS LESS COMMONLY USED FOR STUDYING HYPERTENSION

Although what has been said for blood pressure measurement in rats or dogs also applies generally to other species, some features may differ particularly regarding repeated measurements in chronic experiments.

While both direct and indirect methods have been employed in conscious rabbits, neither method has been applied as described above. Mean aortic pressures have been recorded repeatedly for as long as 6 months by using chronically implanted catheters made of polyethylene tubing (85, 86). But instead of inserting the catheter
through an iliac or femoral artery, the catheter is inserted through a hole in the wall of the aorta (produced by puncture with a sharp needle or trocar) and its outer end, after several coils, is brought out subcutaneously at the neck. Bleeding from the puncture site on the aorta can be controlled by simply pressing on it with a cotton swab and the catheters are claimed to remain in place without requiring sutures. For indirect measurements, a modified Grant-Rothschild pressure capsule (87) is applied to the rabbit's ear to allow interruption of blood flow in the central artery when the capsule is inflated. By placing a lamp behind the ear, obliteration and re-appearance of blood flow can be observed through the translucent membrane of the ear capsule, and systolic (88) as well as diastolic (89) pressures have been recorded. Although diastolic pressures recorded indirectly with the ear capsule agreed closely with those recorded directly from the aorta or central ear artery, the capsular readings tended to overestimate systolic and diastolic pressure by increasing amounts as the blood pressure rose (89). Nonetheless, the procedure was considered useful for estimating systemic blood pressure and for separating normotensive from hypertensive rabbits.

In different types of monkeys, ranging widely from squirrel and rhesus monkeys to baboons, blood pressures have also been measured repeatedly using either direct or indirect methods. Most of the direct methods involve connecting catheters, inserted into the descending aorta or iliac arteries, to a pressure transducer while the conscious monkeys are either seated in a restraining chair (90–93) or maintained on a tether system (94). Uniquely different are the studies done way back in 1978 by Vatner (95) who even then was already using miniature implantable transducers with the leads led externally to back-pack arrangements for radiotelemetry of the pressure signals (71); by thus relying on telemetry to eliminate restraining chairs or tethers he was consequently able to record cardiovascular responses to exercise and excitement in baboons that were conscious and essentially unrestrained. On the other hand, in long-term studies indirect measurements have usually been taken by applying inflatable cuffs on an upper arm (96–98), using the same equipment available for clinical use in man, without bothering to establish the accuracy of such measurements. However, when direct and indirect measurements were actually compared, the pressures obtained have been shown to differ appreciably. In rhesus monkeys of both sexes, pressure readings obtained indirectly with metal cuffs were lower, while those obtained with cloth cuffs were higher, than those recorded directly from the brachial or femoral arteries (99). By contrast, in female baboons, systolic pressures obtained by indirect measurement were found to be more precise than the corresponding diastolic pressures, but indirect systolic pressures were still significantly higher than those recorded directly from the brachial artery (100).

Because cats have not been widely used in hypertension research, papers describing blood pressure measurement in this species have been limited. Geddes (2) found only one report on an indirect method using a tonometer to detect the return of color to the footpad on a hindleg following occlusion with an inflatable annular cuff. Direct measurements recorded in conscious cats from indwelling catheters inserted in the femoral (101) or carotid (102) arteries have also been described, but only for short-term studies. In 1982, an abstract was published (103) describing carotid loops that were kept open for 18 months and from which arterial pressures were recorded repeatedly in conscious cats by direct puncture of the carotid loop.

Finally, although some hypertension research has also been done in pigs (104) by
using direct (105) methods for blood pressure measurement, a tail-cuff method has been validated (106) that may allow repeated measurements in chronic studies on conscious pigs.

IV. SUMMARY AND CONCLUSIONS

Blood pressure can be measured repeatedly in conscious animals by either direct recording from intra-arterial catheters or indirect recording to detect resumption of blood flow in an extremity following occlusion with an inflatable cuff. Direct methods require surgery and are often usable for only a few weeks, while indirect methods, though non-invasive and usable indefinitely, are neither as accurate nor as reliable. For both methods, the general principles of measurement are essentially the same regardless of animal species, but differences between species in body size and anatomy have resulted in unique applications like using the rat’s tail, dog’s hindleg, or rabbit’s ear for indirect measurements. In any species, indirect methods need to be validated carefully before being used and any blood pressure changes detected with such methods should be verified by direct measurement.

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19. Official standards and recommendations: a critical comment

Bernard Waeber, Daniel Hayoz, Michel Burnier, Jürg Nussberger and Hans R. Brunner

Hypertension is a major cause of cardiovascular morbidity and mortality in industrialized countries (1). Treatment of this disease prevents, to a large extent, the occurrence of complications such as stroke, congestive heart failure and chronic renal insufficiency (2). This explains why much effort is currently directed to the detection and treatment of patients with abnormally high blood pressure.

With regard to the management of hypertension, considerable progress has been made during the last decade (3, 4). A number of new antihypertensive drugs acting by different mechanisms are now available, offering the possibility to normalize blood pressure in almost every patient. In contrast, very little has changed with respect to the procedure used to establish the diagnosis of hypertension. The initial and unavoidable step in the clinical approach is the measurement of blood pressure. This key parameter is still obtained routinely by using the sphygmomanometer developed by Riva-Rocci in 1896 (5) and the auscultatory method introduced in 1905 for determining systolic and diastolic pressure (6).

The strongest epidemiological evidence that hypertension constitutes a risk factor is based on blood pressure readings taken conventionally by a doctor. There is however today a growing concern about the reliability of such blood pressure measurements (7). A potential source of error may be the blood pressure measuring device itself. Moreover, false readings can be obtained even with the best equipment if the correct procedure for determining blood pressure is not followed scrupulously. Even more difficult than the technical problems is the recognition of those patients whose blood pressure places them at risk. Many patients exhibit substantially higher blood pressures when facing a doctor than at home or at the work site. This can be demonstrated easily nowadays by non-invasively monitoring ambulatory blood pressure. Which blood pressure should be taken into account in making decisions in the hypertensive patients?
These problems have urged the scientific community to establish official recommendations in an attempt to improve the accuracy of blood pressure measurements and, consequently, to improve the diagnosis and the treatment of hypertension. The subject to be reviewed here is the practical usefulness of the few guidelines currently available.

I. THE NEED FOR ACCURATE BLOOD PRESSURE MEASUREMENTS

Validation procedures for blood pressure measuring devices

Most likely no clinical procedure is performed as frequently as the measurement of blood pressure. Taking a blood pressure is no longer reserved exclusively to doctors or personnel qualified in health care. An increasing number of sphygmomanometers as well as automated or semi-automated devices are now available for patient use. At the same time, non-invasive ambulatory blood pressure monitors are being increasingly used in the evaluation of hypertensive patients. The devices reaching the market are becoming more and more sophisticated and expensive. It appears therefore highly desirable to ask manufacturers to comply with well-defined accuracy criteria before allowing them to market a new device (8).

The requirements for mercury and aneroid sphygmomanometers are clear. Official guidelines on non-automated sphygmomanometers have been provided in the United States by the Association for the Advancement of Medical Instrumentation (AAMI) (9). Standards elaborated by other countries are basically very similar so that it would not appear too difficult to reach an international consensus. Somewhat disturbing, however, is the remaining ongoing controversy surrounding the units to be used for measuring blood pressure. Some would like to see SI units (kPa) adopted or at least displayed side by side with the metric unit on scale (10). Why not stick simply to the millimeter of mercury, this unit having the definite advantage of being tangible and meaningful for the majority of the users? This is certainly the hope in most countries.

The situation is by far more complex with regard to standards for automated blood pressure measuring devices. In this field, the rapidly progressing technology renders necessary some degree of flexibility as well as frequent updating of recommendations. Safety and performance requirements for electronic and electromechanical sphygmomanometers have been proposed by the AAMI in 1987 (11). These standards are particularly pertinent for manufacturers. They give a comprehensive view on all aspects which should be taken into account when developing a new apparatus. The AAMI recommendations are, however, of relatively little help for clinicians who would like to test the accuracy of a device according to a standardized program. For this purpose, the protocol prepared by the British Hypertension Society (BHS) seems more suitable (12). It is a clinically oriented document which lays down pragmatically the steps to follow when evaluating an automated or semi-automated blood pressure measuring device. The entire validation procedure comprises 6 different phases which have to be satisfied successively. Some aspects missing in the AAMI standards, such as interdevice variability and patient acceptability,
are included in the BHS assessment. The principal objective of the BHS Working Party was to prepare general principles for testing non-invasive ambulatory blood pressure monitors. Information in this field has surprisingly been lacking until now, an omission which is difficult to understand considering the large number of portable recorders already on the market or about to be marketed. The BHS report stresses the need to evaluate ambulatory blood pressure measuring systems in conditions of use for which they are primarily designed.

What is the 'gold standard'?

At first glance, it is tempting to refer to intra-arterial pressure as the reference standard. The use of the invasive method for verifying indirect blood pressure measurements has been advocated by the AAMI in the detailed document on electronic or automated sphygmomanometers, but only under stringent conditions since insertion of an indwelling arterial catheter has a small but definite risk of causing complications (11). One may wonder if such comparative studies are really needed since blood pressures measured simultaneously on the same artery by the direct and the indirect techniques are generally not identical (13, 14).

Is there any indication left for the intra-arterial method? In some patients with severe peripheral arteriopathy, it may become impossible, due to the rigidity of their vessels, to obtain reliable blood pressure values. Most of the time the erroneous measurements overestimate the actual pressures prevailing intra-arterially. This phenomenon, known as 'pseudo-hypertension', is mentioned in a recent report of the American Heart Association, but arterial catheterization has not yet been proposed for patients with obvious stiffness of the arterial wall (15).

In fact, the standard mercury sphygmomanometer appears also to be acceptable for the AAMI to validate blood pressure measuring devices, provided the operators are qualified (11). In this respect, the guidelines proposed by the BHS Working Party are even more straightforward, the auscultatory method being considered mandatory to check the accuracy of new automated and semi-automated equipment (12). The BHS gives particular emphasis to the training of the observers, which ought to be completed by a formal assessment. Interestingly, the random-zero sphygmomanometer, although it helps avoid observer bias, should not be employed as a reference standard. This is because this system tends to underestimate pressure systematically (16).

Statistical analysis

The number of data generated during the evaluation of a blood pressure measuring machine is impressive. This is particularly true when the device is an ambulatory blood pressure recorder. It appears necessary, therefore, to gather and analyze the data in a predetermined fashion. The AAMI standards suggest a simple method to compare two sets of blood pressure measurements obtained simultaneously with the test device and the standard technique (11). It suffices to calculate the mean difference (reference reading minus reading of the investigational device) and the corresponding standard deviation. The agreement between the blood pressure values under comparison is considered satisfactory on the basis of a mean difference of
± 5 mmHg with a standard deviation not exceeding 8 mmHg. The AAMI report also favors the calculation of the correlation coefficient, the degree of similitude between two sets of values becoming closer as the correlation coefficient approaches unity. One should be careful, however, not to give too much weight to correlation coefficients when subjecting blood pressure readings to analysis as it often gives excellent concordance while substantial disparities exist between the paired values. This led the BHS Working Party to discard this statistical test (12).

Regarding the quantification of agreement between two sets of blood pressure readings, the option proposed in the BHS protocol is more complicated than that recommended by the AAMI, although still easily applicable (12). The BHS criteria aim not only to verify if a device complies or not with minimum requirements, but also to provide a mode of grading its performance in terms of accuracy. Basically, the differences in blood pressure between the standard sphygmomanometer and the test apparatus are classified in proportion to their magnitude (≤ 5, ≤ 10 or ≤ 15 mmHg). This kind of ranking should allow discrimination, for example, between satisfactory and first-class equipment, which is of course especially relevant for the consumer.

Graphic presentation of the actual blood pressure values deriving from the analysis may be more informative than trying to characterize the data statistically. For many years, it was customary to plot the blood pressure readings obtained with a reference device against those determined with the apparatus under evaluation. This approach was almost invariably followed by calculation of the correlation coefficient. To illustrate the problems associated with this approach an illustration based on a hypothetical data set derived from a validation procedure carried out in 25 subjects is shown in Figure 1 which depicts the scatter plot for the two sets of systolic blood pressures. The points appear quite well clustered around the line of identity and the correlation coefficient is highly significant. The mean difference between the paired measures averages 3.2 mmHg, with a standard deviation of 7.6 mmHg. The test device would comply, therefore, with the requirements of the AAMI.

Fig. 1. Relationship between systolic blood pressures (mmHg) measured simultaneously with a reference (abscissa) and a test (ordinate) device.
Fig. 2. Relationship between systolic blood pressures (mmHg) measured with a reference device (abscissa) and the difference existing between this value and a blood pressure reading taken simultaneously with a test device (ordinate).

Another method of evaluating the data is to represent the differences between the reference readings and the corresponding values obtained with the test device in relation to the reference blood pressure levels (17). Figure 2 depicts such an analysis using the same data as in Figure 1. The discrepancies between the two sets of blood pressures are now evident. Most of the readings do not differ by more than 5 mmHg as long as the reference blood pressure is below 140 mmHg. The difference between the two types of blood pressure measures tends, however, to increase as the reference blood pressure rises. Such an observation illustrates immediately the need to extend the verification of the test device to a higher range of reference pressures. In fact, the BHS Working Party demands very strongly this latter type of assessment (12).

II. WHO SHOULD VALIDATE BLOOD PRESSURE MEASURING DEVICES?

It is the responsibility of manufacturers as well as of health authorities to guarantee that the blood pressure measuring machines reaching the market are safe and reliable. For both partners, there exists an urgent and imperative need for a broad, if possible worldwide, harmonization of regulations to be followed before marketing a new apparatus. Unfortunately, in most countries, the test requirements discussed above are carried out only on a voluntary basis, which means that they do not have to be adopted necessarily by manufacturers.

How can this situation be improved? A task force enrolling health care specialists and representatives from concerned industries could be instituted with the aim of preparing standards acceptable ubiquitously. This working committee could act with the support of government regulatory authorities and major international medical societies. The AAMI and BHS standards would certainly serve as a strong basis for the establishment of a concensus document. The manufacturers would
then know exactly what to do when developing a new blood pressure measuring device. Independent evaluation of the test apparatus would be required in 2 or 3 institutions chosen by the manufacturer from a list of approved, competent centers. This ideal is not completely unrealistic. On first view, the organization of such a large working group may seem very expensive. In the long run, however, this concentration of medical, legislative and industrial efforts should make it possible to save money. Even more important, this approach would ensure that the reliability of devices on the market had been adequately tested.

III. IS IT ENOUGH TO MEASURE BLOOD PRESSURE ADEQUATELY?

Let us assume that a doctor possesses a blood pressure measuring device which fulfills the most rigorous requirements, and that the apparatus is used properly so that all potential pitfalls are avoided. Let us then suppose that that doctor repeatedly finds at intervals of several weeks abnormally high pressures (> 160/95 mmHg) in a middle-aged patient with no evidence of target organ damage. The doctor will have no difficulty in justifying the initiation of a life-long antihypertensive therapy by referring to official guidelines. Is there any way for improving this mode of decision making? Several points should be considered before such a decision. First, the definition of hypertension implies that, beyond a certain blood pressure level, patients should be advised to have treatment so as to restore their risk to the so-called ‘normal’ acceptable risk of developing a cardiovascular complication (18). The second consideration is that blood pressure is prone to substantial circadian variations with the highest values occurring during the daytime and the lowest during sleep (19). Moreover, blood pressure can fluctuate markedly depending on activities at work and the degree of physical or mental stress (20). It therefore appears very naive to presume that blood pressures measured casually in the doctor’s surgery are a good representation of those prevailing during daily activity. This is particularly true if one considers that the presence of a doctor may by itself induce a transient, more or less pronounced, blood pressure rise in a number of patients (21–23). Self-monitoring of blood pressure at home and intermittent, non-invasive recording of blood pressure during the patient’s daily routine have provided considerable understanding of these fluctuations in blood pressure. (24–27).

The scientific community has to deal now with a new problem. Do self-determined blood pressures and ambulatory blood pressures yield more reliable information about the cardiovascular risk of an individual patient than does the conventional blood pressure measurement obtained by a doctor? This key issue has been addressed in several cross-sectional retrospective studies. The results were unanimous in indicating that blood pressure readings taken outside the medical environment provide a more accurate prediction of the risk of future cardiovascular complications than blood pressures determined by a doctor (28–32). These findings have unfortunately still not been verified in prospective trials. Ethical considerations probably make the performance of a large-scale intervention study aimed at characterizing the cardiovascular risk of self-monitored and ambulatory recorded pressures very difficult, if not impossible. All should be aware of the background of uncertainty linked with the evaluation of blood pressure outside the doctor’s
surgery. This should be endorsed by the well-established fact that a considerable number of patients do not benefit from antihypertensive therapy when the diagnosis of hypertension is made solely on blood pressure readings taken by a doctor (33). Several consensus papers published during the last few years discuss, in more or less detail, the potential usefulness of self-measured and ambulatory recorded blood pressures (3, 15, 34–36). None of these documents provides clear guidelines as to how these blood pressures ought to be taken into account in the diagnosis and the treatment of hypertension. There is therefore an urgent need for standards not only with regard to blood pressure measuring machines, but also with respect to the final interpretation of the measurements obtained with these devices. Very recently, however, a comprehensive document on ambulatory blood pressure monitoring has been prepared by a national working group in the United States (37). In this report, a number of clinical circumstances, for the evaluation of which the use of ambulatory blood pressure monitoring is particularly recommended, have been selected.

IV. CONCLUSIONS

The market for blood pressure measuring machines is still expected to rise during the last decade of this century. With the advent of an increasing number of new devices, there is an obligation for health authorities, medical societies and manufacturers to elaborate standards with the ultimate goal of achieving worldwide acceptance.

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20. The future

Eoin O’Brien and Kevin O’Malley

The thing that hath been, it is that which shall be;
and that which is done is that which shall be done;
and there is no new thing under the sun.

(Ecclesiastes i.2)

I. THE PAST IS PROLOGUE

This book began with a review of the historical developments in blood pressure measurement, a review that alluded to the failure of contemporary researchers in hypertension to stand on the shoulders of their predecessors. And so shall we end; acknowledging our weaknesses and anticipating that the same charges may well be laid against us by those who come after. Can we hope, perhaps, that hindsight by endowing us with some prescience will enable us to avoid such pitfalls?

Our generation possesses a facility that Hales, Ludwig, Marey, Mahomed, Riva-Rocci, Janeway and Pickering (see Chapter 1) were denied, namely the technology not only to measure blood pressure, but also to detect subtle end-organ changes resulting from hypertension, sometimes even before blood pressures becomes elevated. Whether or not we are possessed of the wisdom and originality of thought that would have not been wanting in, for example, Janeway and Pickering which is so necessary to advance medical science, remains to be seen. The signs to-date are not encouraging. We have often failed to lay down the goals of research and where we have identified these, e.g. the need for longitudinal studies in ambulatory measurement, we have often been painfully ineffective in enacting the necessary policy. There are, however, some promising signs most especially in the international sharing of ideas and resources as evidenced, for example, in the first International Consensus Conference on Indirect Ambulatory Blood Pressure Monitoring in Berlin (1) in March 1990 (to be followed by a second meeting in Dublin in 1991) and the multicenter European study on Systolic Hypertension in the Elderly (Syst-Eur) which has a side-project on ambulatory blood pressure measurement (2).

Looking to the future, certain advances seem almost inevitable whereas others will require careful planning if they are to be realized.
II. CONVENTIONAL MEASUREMENT

Conventional measurement with an observer using a mercury sphygmomanometer remains, perhaps surprisingly in this, the technological age, the yardstick against which other techniques must be assessed (3). There are many disadvantages to the technique, not least being its dependency on observers (4) and the health hazard presented by mercury (5). It cannot be long before accurate semi-automated devices become available thus removing one of the major sources of inaccuracy — the observer. Until such time every effort must be made to improve the accuracy of the technique and in hypertension research a program of training and assessment of observers in essential (6).

The inadequacy of bladder size is a major cause of inaccuracy of conventional sphygmomanometry for which we, as practitioners, are largely responsible by having permitted manufacturers to modify this component without consideration of the consequences for accuracy. Manufacturers must be persuaded, therefore, to provide cuffs with inflatable bladders measuring $35 \times 12$ cm for adult arms (7). A more profound lesson for the future is the need for greater cooperation between medical practice and the manufacturing industry so that modifications to devices and components are not made without consultation or notification.

III. RESEARCH SPHYGMOMANOMETRY

The concept of a sphygmomanometer for research that would reduce observer bias and digit preference and thereby improve observer accuracy as proposed by Rose (4) resulted in the invention of the London School of Hygiene (4) and Hawksley random-zero (8) sphygmomanometers. Unfortunately both devices have been shown to be inaccurate (9, 10), but it should be possible for manufacturers to correct these inaccuracies and restore these useful sphygmomanometers to medical research.

IV. SEMI-AUTOMATED AND AUTOMATED SPHYGMOMANOMETRY

Despite the availability of a large variety of semi-automated and automated sphygmomanometers we do not know of any validation studies that make it possible to recommend a replacement for the mercury sphygmomanometer (11). Some of the devices used for ambulatory blood pressure measurement have come close to the mercury sphygmomanometer (12) and whereas such devices would be too expensive for conventional requirements, the existence of such systems is evidence of the technological ability to provide accurate automated sphygmomanometers. The advent of an accurate automated sphygmomanometer will also facilitate the validation procedure for new devices and reduce the costs of such evaluations in that it will be possible to dispense with observers (13).

Another area of future development dependent on improved automated sphygmomanometry is the measurement of blood pressure during exercise (see Chapter 9).
V. AMBULATORY BLOOD PRESSURE MEASUREMENT

Undoubtedly the greatest advances in blood pressure measurement in the future will be in ambulatory techniques for monitoring blood pressure over 24 hours and longer periods. Cheaper, more accurate, smaller, noiseless systems with improved energy sources may be anticipated (14).

*Intra-arterial techniques*

The impetus given to the study of circadian profiles of blood pressure by intra-arterial measurement must be acknowledged (see Chapters 1 and 6), but in so doing we must also acknowledge its unsuitability as a technique for general use. Such are the potential complications of the method that ethical considerations dictate that its role in future must be confined to a few specialized centers (15) and even then only for clearly defined objectives that cannot be achieved using non-invasive techniques.

*Intermittent versus continuous measurement*

A major limitation of the present generation of ambulatory recording systems is their capability to provide only intermittent measurements of blood pressure over a 24-hour period, and to achieve this, activity has to be interrupted so that accurate recordings may be obtained. It may be anticipated that the next generation of ambulatory systems will provide continuous recording of ambulatory blood pressure without the need to cease activity and thereby come closer to yielding data similar to that from direct intra-arterial systems. In fact, techniques based on the vascular unloading principle of Peñáz, now in the development phase, show promise in this regard (16).

*Simultaneous ECG recording*

Most ambulatory systems provide the facility for simultaneous measurement of blood pressure and heart rate and at least one system has the facility for simultaneous recording of the ECG. It may be anticipated that with improving technology, this facility will become more widely available in the future.

*Assessment of activity*

The potential importance of nocturnal blood pressure in the management and prognosis of hypertension (17) calls into question our ability to relate activity and sleep to blood pressure changes (18). The development of motion-logging devices is an interesting area of research which should in time replace the subject diary which has so many limitations. Perhaps then the way will lie open for devising techniques for the simultaneous measurement of stressful situations.

*Data analysis*

The statistical analysis of data provided by blood pressure measurement is a com-
plex subject which has been given due attention recently (see Chapters 10 and 15). However difficult such analyses may be for conventional methods of measurement, the problem is amplified by the large amount of data provided by ambulatory measurement. This topic is likely to demand much thought and endeavor in the future (19).

*Normal values*

Without being aware of the normal reference values for 24-hour ambulatory measurement the application of the technique to clinical practice must be seen as premature. The importance of this topic has been recognized (see Chapter 11) (20), and a number of population-based studies are presently being published which should clarify this issue (21).

*Prognostic value of ambulatory blood pressure*

One of the most exciting aspects of ambulatory measurement is its apparent superiority to conventional measurement in assessing prognosis (22–24). One of the most pressing requirements of future research is the establishment of carefully planned longitudinal studies to determine the exact role of ambulatory *vis-à-vis* conventional measurement in hypertension management (25).

*Assessment of antihypertensive drug effect*

The role of ambulatory measurement both in assessing antihypertensive drug effect in the individual patient and in research studies of antihypertensive drug efficacy has been the subject of a number of recent reviews, all of which illustrate the value of the technique in not alone determining the onset, duration and termination of drug effect, but also its potential for reducing trial sample size and thereby making it possible to determine antihypertensive drug efficacy in small numbers of patients (26–29). The advantages of 24-hour ambulatory blood pressure measurement are such that the technique should be incorporated in the protocols of all studies seeking to determine the blood pressure lowering effect of antihypertensive drugs.

*Cost/benefit*

Ambulatory measurement is an expensive investigation, but against this cost must be balanced the large saving in drug prescribing that results from identifying those individuals with ‘white coat hypertension’ (30) who may not need treatment and by adjusting drug treatment to suit the individual response to antihypertensive medication throughout the 24-hour cycle (29). The subject of cost/benefit analysis is complex (31) involving many aspects of health care management and economics, but it is one which should be addressed without delay.
VI. RECOMMENDATIONS FOR BLOOD PRESSURE MEASUREMENT

National bodies must continue to up-date their recommendations on blood pressure measurement (7, 32) so as to keep practitioners alert to the problems associated with blood pressure measurement, but there must surely be a case now for directing our energies towards establishing joint policies that might serve as international recommendations.

VII. VALIDATION OF DEVICES

The need for a standardized approach to the evaluation of new systems and techniques of blood pressure measurement is now accepted (15, 33) and the Association for the Advancement of Medical Instrumentation in the U.S. (34) and the British Hypertension Society in the U.K. (35) have each drawn up protocols for evaluating the accuracy of automated and semi-automated devices. The call for editors of hypertension and pharmacological journals to evaluate critically the assessment of devices used in research work submitted for publication (33) may be expected to encourage manufacturers to ensure that independent validation studies are performed by reputable laboratories prior to marketing of blood pressure measuring devices. As with recommendations for blood pressure measurement, there is also a strong case for more international cooperation in the production of equipment validation standards, an eventuality which will no doubt become more realizable with harmonization of equipment standards in the European Community (36).

We close this volume, therefore, on a note of optimism for the future, optimism born out of a comparatively new phenomenon in medical research, namely that of cooperation between groups working in different countries, each willing to share ideas and resources with the other in the advancement of medical science. The cooperation of our co-authors in the production of this volume is surely testimony to this welcome trend.

REFERENCES


APPENDIX I

British Hypertension Society recommendations on blood pressure measurement

OBSERVER

Only an observer who is aware of the factors that lead to false readings should measure blood pressure. Wrong readings obtained through failure to use the proper technique often lead to the wrong diagnosis, which may result in unnecessary or inappropriate treatment and follow up. Observer accuracy is often taken for granted and when doctors and nurses are assessed critically there is often a surprising degree of inaccuracy. A video film is now available from the British Hypertension Society for training observers and assessing their accuracy.

The aim of these recommendations is to provide simple guidelines for the indirect measurement of blood pressure.

EQUIPMENT

Two instruments are required for measuring blood pressure: a sphygmomanometer and a stethoscope.

The sphygmomanometer consists of a manometer, an inflatable bladder in a cuff, and an inflation—deflation device. Before any measurement is attempted the equipment must be checked to make sure that it is appropriate and in good order. If any part of the apparatus is defective or unsuitable, alternative equipment must be used.

Reprinted by courtesy of the British Hypertension Society and the British Medical Journal, Tavistock Square, London. It is recommended that the booklet from which this Appendix is taken is used in conjunction with the British Hypertension Society video Blood Pressure Measurement published by the British Medical Journal in 1990.
These recommendations were prepared by a working party of the British Hypertension Society: J.C. Petrie, University of Aberdeen; E.T. O'Brien, Beaumont Hospital, Dublin; W.A. Littler, University of Birmingham; M. de Swiet, Royal Postgraduate Medical School, London; P.L. Padfield, University of Edinburgh; M.J. Dillon, Hospital for Sick Children, London.
Incorrect technique → False readings
→ Unnecessary treatment, inappropriate treatment and follow up

Points to check in assessing equipment

**Manometer** — visibility of meniscus; calibration
**Cuff** — condition; length and width of inflatable bladder
**Inflation-deflation device** — possible malfunction; control valve
**Stethoscope** — condition
**Maintenance** — regularity responsibility

**Manometer**

*Mercury column*  The meniscus should be clearly visible, not obscured by oxidised mercury on the inside of the glass. Before inflation it must be at zero.

*Aneroid*  This type loses its accuracy over time, leading usually to falsely low readings and a consequent underestimation of blood pressure. The accuracy of the instrument may be checked at different pressure levels by connecting it with a Y piece to the tubing of a standardized mercury column manometer. If recalibration is necessary this must be done by the manufacturer.

**Cuff**

The cuff consists of an inflatable bladder within a restrictive cloth sheath. The bladder, tubing, connections, inflation bulb, and valves should all be sound. The sheath containing the bladder should also be in good condition and have a secure fastening. Provided it is long enough to wrap round the arm and be easily secured, the length of the sheath is not important.

![Bladder length at least 80% of circumference of arm]

The length of the bladder is one determinant of the area of pressure applied to artery. If the bladder is too short the blood pressure will be overestimated, since the pressure is not fully transmitted to the artery. The bladder should nearly or completely encircle the patient's arm, and the length should be at least 80% of the circumference of the arm. Most commercially available bladders are only 23 cm long.
and with such short cuffs the centre of the bladder must be positioned directly over the artery. For normal adult arms a 35 cm bladder is strongly recommended; that will fully encircle most adult arms, but for a few adults with heavily muscled or obese arms longer bladders — up to 42 cm — may be necessary. Alternatively, a 35 cm long bladder placed over the brachial artery will give accurate measurements for people with heavily muscled or obese arms.

The width of the bladder determines the length of the segment of artery to be occluded. Too narrow a bladder leads again to overestimation of blood pressure for the same reason that too short a one does; but the error is not likely to be as great as that resulting from the use of bladders that are too short. In adults bladder widths greater than 12.5 to 13 cm may encroach on the antecubital fossa and interfere with auscultation.

A bladder with the dimension 12.5 × 35 cm is therefore recommended for blood pressure measurement in adults.

The dimensions of the bladder should be clearly shown on each cuff, together with a prominent marker indicating the centre of the bladder.

**Inflation – deflation device**

Failure to achieve a pressure of 40 mmHg above the estimated systolic blood pressure or 200 mmHg after 3 – 5 seconds of rapid inflation is a sign of equipment malfunction. So too is the inability of the equipment to deflate smoothly when the controlling release valve is operated at 2 – 3 mm/s or at each pulse beat. When such problems occur the unit should be set aside and clearly marked with instructions for detective parts to be repaired or replaced. Faulty control valves, leaks, dirty vents, and perished tubing are simple to repair. The commonest source of error in the inflation – deflation system is the control release valve, which can easily be replaced.

Deflation that is either jerky or too rapid may result in the systolic pressure being underestimated and the diastolic pressure overestimated. If, on the other hand, deflation is too slow the patient may suffer pain, even bruising, and blood pressure may be overestimated.

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**Recommended bladder dimensions**

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Subject</th>
<th>Maximum arm circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 × 4 cm</td>
<td>Small children</td>
<td>17 cm</td>
</tr>
<tr>
<td>18 × 8 cm</td>
<td>Medium sized children</td>
<td>26 cm</td>
</tr>
<tr>
<td>35 × 12.5 cm</td>
<td>Grown children and adults</td>
<td>42 cm</td>
</tr>
</tbody>
</table>

Accurate readings may be obtained in adults with arm circumferences greater than 42 cm by placing a cuff with a 35 cm bladder so that the centre of the bladder is over the brachial artery.
Hospital sphygmomanometers
Responsibility for maintenance clearly defined
Date for routine 6-monthly service marked on unit
Defective equipment reported to member of staff responsible
Replacement parts and instruction booklet available in clinical area

Sphygmomanometers in surgeries
Check at least once a year; more frequent checks may be required for aneroid models

Stethoscope
The stethoscope should be a good quality one in good condition with clean, well fitting earpieces.

Maintenance
The date of last maintenance or recalibration should be clearly marked on the sphygmomanometer, together with the date when the next is due. Sphygmomanometers used regularly in hospitals should be routinely serviced every six months. Those in less frequent use should be checked once a year. Replacement parts are cheap and should be readily available in the clinical area, together with a maintenance instruction booklet.

The responsibility for reporting faulty equipment or the lack of appropriate cuffs lies with the observer, who should always refuse to use defective or inappropriate equipment. The responsibility for arranging regular maintenance should be clearly defined for each clinical area.

PROCEDURE
Those who measure blood pressure should be familiar with the practical points listed and discussed below.

Explanation to patient
The observer should outline the procedure briefly. In particular, he or she should warn the patient of the minor discomfort caused by inflation and deflation of the cuff and tell the patient that the measurement may be repeated several times.

Defence reaction
The defence reaction is the rise in blood pressure associated with the anxiety of measurement. This increase in blood pressure tends to subside once the patient becomes accustomed to the procedure and the observer, but in many patients blood
pressure is always higher when measured by doctors (and nurses) — so called 'white coat hypertension'. Readings are likely to be lower when they are taken in the home or by ambulatory measurement. Except in patients with severe hypertension, repeated measurements to assess the severity of raised blood pressure should be made every one or two weeks for at least a month. Changes in drug treatment should not be made on the basis of one measurement but rather on the patterns of blood pressure change during a period of observation. In many patients blood pressure falls without treatment.

**Variability in blood pressure**

Blood pressure varies in individuals according to the time of day, meals, smoking, anxiety, temperature, and the season of the year. It is usually at its lowest during sleep.

**Posture of patient**

Whether the patient is sitting or lying-(supine) makes no difference to the blood pressure readings. Pressure should also be measured in the standing position in patients whose symptoms or drug regimen may be associated with a disproportionate postural fall. Pregnant patients may suffer a profound fall in blood pressure when lying supine; therefore in pregnancy all measurements should be performed with the patient either sitting or in the left lateral position. No information is available on the optimal time in the position before the measurement, but we suggest three minutes lying or sitting and one minute standing.

**Position of arm**

The arm should be horizontal and supported at the level of the mid-sternum because dependency of the arm below heart level leads to an overestimation of systolic and

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**Practical points**

- Explanation to patient
- Defence reaction
- Variability in blood pressure
- Posture of patient
- Position of arm
- Application of cuff
- Position of manometer
- Estimation of systolic pressure
- Auscultatory measurement of systolic and diastolic pressure
- Number of measurements
- Indications for measurement in both arms
- Times of measurement
- Measurement in children
- Leaflet advice
diastolic pressures of about 10 mmHg. Correspondingly, raising the arm above the heart level leads to underestimation of these pressures.

Application of cuff

The patient should be in a warm environment. Tight or restrictive clothing should be removed from the arm. A simple measure is to request that patients wear a short sleeved garment when attending for blood pressure measurement.

The position of maximal pulsation of the brachial artery in the arm, just above the antecubital fossa, may be marked lightly with a pen. A cuff with a long enough bladder should then be applied to the upper arm. The tubing may be placed superiorly so that it does not interfere with auscultation. The centre of bladders less than 35 cm long must be positioned over the line of the artery. The lower edge of the bladder should be 2–3 cm above the marked point. The cuff should fit firmly and comfortably and be well secured.

Position of manometer

In the mercury column manometer the column must be vertical (unless designed with a tilt), at eye level, and not more than three feet from the observer. Stand mounted manometers are recommended, largely because they are mobile and easily adjusted for height. Box and desk models are more easily damaged and less convenient to use.

Estimation of systolic pressure

The systolic pressure should be estimated before the operator uses the stethoscope by palpating the brachial artery pulse and inflating the cuff until the pulsation disappears. The point of disappearance represents the systolic pressure. This technique is especially useful in patients in whom auscultatory end points may be difficult to judge accurately — for example, pregnant women, patients in shock, or those taking exercise.

Auscultatory measurement of systolic and diastolic pressures

The stethoscope is placed gently over the artery at the point of maximal pulsation. It must not be pressed too firmly or touch the cuff, or the diastolic pressure may be underestimated. The presence is then raised by inflating the bladder to 30 mmHg above the systolic blood pressure as estimated by palpation. Next the pressure is reduced at 2–3 mmHg per second, or pulse beat. The point at which repetitive, clear tapping sounds first appear for at least two consecutive beats giving the systolic blood pressure. The point where the repetitive sounds finally disappear gives the diastolic blood pressure (phase 5). Both measurements should be taken to the nearest 2 mmHg.

In some groups — for example, children and pregnant, anaemic, or elderly patients — sounds may continue until the zero point. In such patients the point at which the repetitive sounds become muffled (phase 4) is taken as the diastolic
pressure. The point of muffling is usually higher than the true arterial diastolic pressure. If phase 4 is used this should be clearly recorded (200/90 mmHg — phase 4).

Digit preference, whereby observers choose to record, say, only to the nearest 0 to 5 mmHg, is another source of bias. It is important to realise that such digit preference may introduce substantial errors that could lead to incorrect decisions being made, especially in patients with borderline blood pressures. Such bias is best avoided by recording to the nearest 2 mmHg.

The silent or auscultatory gap occurs when the sounds disappear between the systolic and diastolic pressures. Its importance is that unless the systolic pressure is palpated first this pressure may be underestimated. The presence of a silent gap should be recorded on the case sheet or blood pressure chart.

**Number of measurements**

It is preferable to take one measurement carefully at each visit, repeating the measurement if there is uncertainty or distraction, rather than making a number of hurried measurements. For patients in whom sustained increases of blood pressures are being assessed a number of measurements should be made on different occasions before diagnostic or management decisions are made.

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**Systolic pressure estimation**

1. Palpate brachial artery pulsation
2. Inflate cuff until pulsation vanishes
3. Deflate cuff
4. Take reading

**Systolic and diastolic pressure measurements**

5. Place stethoscope gently over point of maximal pulsation of brachial artery
6. Inflate cuff to 30 mmHg above estimated systolic pressure
7. Reduce pressure at rate of 2–3 mmHg per second or per pulse beat
8. Take reading of systolic pressure when repetitive, clear tapping sounds appear for two consecutive beats
9. Take readings of diastolic pressure when repetitive sounds disappear

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**Sustained blood pressure elevation**

Make a number of measurements at different visits

Make each measurement carefully
Indications for measurement in both arms

Blood pressure should be measured in both arms in all patients with raised blood pressure at the initial assessment, and if there is a reproducible difference of 20 mmHg for systolic pressure and 10 mmHg for diastolic pressure simultaneous measurement should be performed. Simultaneous measurement in both arms is also indicated in patients with suspected coarctation of the aorta where local anatomical abnormalities are suspected.

Times of measurements for patients taking drugs that lower blood pressure

In patients taking drugs that lower blood pressure the optimum time for control measurements will depend on the time of day at which the drugs are taken. It may therefore be helpful, when assessing the effect of antihypertensive drugs, to note the time of drug ingestion in relation to the time of measurement.

Obtaining a blood pressure profile

Accurate though measurement may be when the above recommendations are followed, it should be realised that any such measurement represents only a fraction of the 24-hour blood pressure profile. The increasing use of 24-hour ambulatory blood pressure measurement in clinical practice has shown a number of patterns of blood pressure behaviour, such as the ‘white coat’ effect whereby the circumstances of measurement may in themselves induce a rise in blood pressure. It is, therefore, important to attempt to obtain a profile of blood pressure behaviour. This may be achieved most comprehensively by 24-hour ambulatory measurement, but repeated measurements of blood pressure at successive visits and home recording also give helpful information on blood pressure behaviour.

For the future, careful measurement of blood pressure with a mercury sphygmomanometer following the above recommendations is likely to remain the most effective first line in assessing blood pressure. If conventional measurement is below 150/90 mmHg, especially over a number of measurements, that individual may be passed as normotensive. If, however, blood pressure is elevated above this level an assessment of blood pressure behaviour should be obtained before diagnostic and therapeutic decisions are made.

Leaflet advice

Patients with high blood pressure should be given a leaflet stressing that blood pressure elevation is only one risk factor for cardiovascular disease. Giving up cigarettes, reducing alcohol consumption, weight reduction, and dietary restriction of cholesterol and fats, may be as important as lowering blood pressure.

Coarctation of aorta or suspected anatomical abnormalities

Measure simultaneously in both arms
The following should be your goals
1. If your smoke — Stop now
2. Your ideal weight body is ...........................................................
3. To achieve this your total daily calorie intake should not exceed ....................
4. If your diet is high in cholesterol — reduce your consumption of cholesterol rich foods
5. Do not add salt to food at table
6. Take regular exercise
7. If tablets are prescribed take these as instructed and never stop tablets without consulting your doctor

The successful management of blood pressure depends on cooperation between the patient and the doctor.

What is blood pressure?
Everyone has a certain level of blood pressure. It is the force of the blood from the heart against the walls of the arteries. About one in five adults develop high blood pressure for reasons that are not fully understood, and this is often called hypertension.

High blood pressure means that the heart has extra work to do and it increases in size to overcome the pressure. Also the blood vessels thicken to contain the higher pressure of the blood. This reaction in the heart and blood vessels leads to heart disease, and vascular disease such as stroke.

What is normal blood pressure?
Blood pressure is measured with a sphygmomanometer which gives two pressure levels in millimetres of mercury — written as mmHg; the high level is the systolic pressure and the low level is the diastolic pressure.

Blood pressure varies considerably with activity, emotion, stress, age and a number of other factors, but in adults persistent elevation of pressure above 150/90 (Systolic/Diastolic) mmHg is an indication for medical advice.

CONCLUSIONS

• The measurement of blood pressure is one of the most commonly performed procedures in clinical medicine and should not be done carelessly.
• Defective or inappropriate equipment must not be used. A phased maintenance programme is essential and inexpensive.
• A maintenance programme should be defined for each clinical area where blood pressure measurements are made.
• The main cause of misleading readings should be highlighted in training.
• All those who measure blood pressure should be assessed on the practical aspects of the procedure.
APPENDIX II

British Hypertension Society recommendations on measurement of blood pressure in children

This report follows the previous recommendations of the British Hypertension Society on blood pressure measurements in adults (1) and considers the techniques for measuring blood pressure in children and the circumstances in which blood pressure might be measured.

MEASUREMENT TECHNIQUES

The only technique that is practicable for widespread clinical application is conventional sphygmomanometry with a well maintained mercury sphygmomanometer. Measurement of systolic blood pressure is preferred to diastolic blood pressure because of its greater accuracy and consistency. The choice of the correct cuff is crucial. To cover the age range 0–14 years a minimum of three cuffs is necessary; recommended bladder sizes are 4 × 13 cm, 8 × 18 cm, and 12 × 35 cm (adult cuff). The widest cuff that can be applied to the arm should be used. The length of the inflation bladder should be at least two thirds of the circumference of the arm and preferably longer. Secure fastening is essential; this may not be possible with Velcro, especially when using the smaller cuffs.

In some healthy children aged under 5 years and all children aged under 1 year measurement of blood pressure by conventional sphygmomanometry is impossible because the Korotkov sounds cannot be heard reliably. In these children and children who are in shock or who have low cardiac outputs more sensitive detection systems such as Doppler ultrasound or oscillometry should be used.


These recommendations were prepared by a working party of the British Hypertension Society: M. de Swiet, Royal Postgraduate Medical School, London; M.J. Dillon, Hospital for Sick Children, London; W. Littler, University of Birmingham; E. O'Brien, Beaumont Hospital, Dublin; P.L. Padfield, University of Edinburgh; and J.C. Petrie, University of Aberdeen.
CIRCUMSTANCES OF MEASUREMENT

Except in acutely ill children blood pressure should be measured after the child has been sitting quietly (or lying if aged under 2 years) for at least three minutes. Measurements made when the child is eating, sucking, or crying will be unrepresentative and usually too high. Decisions about the child’s management should not be taken on the basis of measurements of blood pressure taken on a single occasion.

NORMAL VALUES

At the age of 4 days the median systolic blood pressure is 75 mmHg (95th centile 95 mmHg) and at 2 years the median is 95 mmHg (115 mmHg). Between the ages of 2 and 14 years blood pressure changes little; body size (represented by body length) is a better criterion by which to judge the normality of blood pressure measurements. Figure 1 shows the relation of blood pressure to body length. More complex functions of height and weight have been used to adjust blood pressure, but for clinical purposes height alone is adequate and simple to use. The increase in height at puberty compensates for the increase in blood pressure occurring at that age. After the age of 14 the criteria applied to adults should be used for assessing blood pressure.

INDICATIONS FOR MEASUREMENT

Sick children should have their blood pressure measured whenever a general medical examination is indicated.

Fig. 1. Relation of blood pressures to height in children. Figures are percentages of boys and girls. Data redrawn with permission from André et al. (2).
The following groups of children should have regular blood pressure measurements: (a) those who have been found to have high blood pressure on a previous occasion, (b) those with any disease of the kidneys, ureters, or bladder, and (c) those with diabetes.

Screening for blood pressure is probably not justified. Blood pressure in children is very variable. Measurements of blood pressure in the community have suggested that at most only 1% of children have blood pressures consistently and appreciably greater than the 95th centile for single measurements. Children with a family history of hypertension, however, may be at greater risk. By extrapolation from results in adult hypertension, children with severe primary hypertension and with secondary hypertension are likely to benefit from investigation and treatment, but the cost–benefit ratio from identifying these by screening is not clear. At present, population screening to identify children with ‘hypertension’ is not recommended.

REFERENCES

APPENDIX III

American Heart Association recommendations for human blood pressure determination by sphygmomanometers

INTRODUCTION

Blood flow to the tissues of the body is maintained by the pumping action of the heart. As the left ventricle contracts during systole, blood is ejected into the aorta and arteries in the periphery; the pressure in these vessels rises sharply to a peak level, the systolic pressure (SP). Then, as the left ventricle relaxes during diastole, the pressure in the aorta and peripheral arteries falls gradually to a trough level, the diastolic pressure (DP). These pressures have been traditionally recorded in millimeters of mercury (mmHg) and noted as SP/DP. The systolic pressure in the lower extremities may be 20–30 mmHg higher than in the upper extremities, whereas the diastolic pressure is usually similar in both extremities. The pulse pressure is the difference between the systolic and diastolic pressures and normally is in the range of 50 mmHg. As the pressure rises in the aorta, a pulse wave is generated and propagated throughout the arterial tree; this pulse wave changes in contour from the aorta to the arteries and capillaries. The mean arterial pressure is the average pressure throughout the cardiac cycle or the mean integrated pressure of the area under the arterial pressure curve. This may be derived from indirect pressure measurements as the sum of the diastolic plus one third of the pulse pressure.

Reproduced with permission. © 'Recommendations for Human Blood Pressure Determination by Sphygmomanometers,' 1987. Copyright American Heart Association. Report of a Special Task Force Appointed by the Steering Committee, American Heart Association; Edward D. Frohlich, Chairman; Carlene Grim; Darwin R. Labarthe; Morton H. Maxwell; Dorothee Perloff; William H. Weidman; Members.
MEASURING BLOOD PRESSURE

The level of arterial pressure is an important index of present cardiovascular function and risk of future cardiovascular morbidity and mortality. The lower the systolic and diastolic pressures, the better the long-term prognosis for cardiovascular health (1). Thus, unless the patient is in a clinical state of shock (see page 412) or is affected by a disease that may lower arterial pressure (e.g., blood loss, myocardial infarction), there are no adverse implications or effects of what has been commonly referred to as ‘low blood pressure.’ In contrast, the higher the systolic and diastolic pressures, the greater is the cardiovascular risk of increased morbidity and mortality.

METHODS OF MEASURING BLOOD PRESSURE

Direct measurement of blood pressure

Blood pressure can be measured directly by inserting a needle or catheter into the arterial tree and connecting it to a calibrated pressure transducer for continuous measurement of the beat-by-beat arterial pressure. However, this technique is impractical for the measurement of blood pressure in nonhospitalized patients; hence, the indirect or occluding-cuff auscultatory technique is recommended for most clinical circumstances. This Appendix describes the technique recommended by the American Heart Association for indirect measurement of blood pressure, the common errors and pitfalls that may be encountered, and methods for increasing its accuracy. This edition is the fifth revision of the standards first proposed in 1939 (2–5).

Indirect measurement of blood pressure

Blood pressure is measured indirectly by the use of a sphygmomanometer, which consists of a compression bladder that is enclosed in an unyielding cuff, an inflation bulb or other device that increases pressure in the bladder of the occluding cuff, a manometer that indicates the applied pressure, and a controllable valve on the inflation bulb that deflates the cuff. A stethoscope is the other instrument necessary for indirect measurement of pressure.

Indirect methods for measuring blood pressure are based on the occluding-cuff auscultatory technique, based on work by Riva-Rocci (1896), Hill and Barnard (1897), and Korotkoff (1905). A nondistensible cuff containing an inflatable bladder is placed over the brachial artery. Rubber tubing connects the bladder to a valved rubber bulb that permits bladder inflation and to a manometer or gauge that reflects the pressure within the bladder in the occluding cuff. The bladder is inflated and, when its pressure exceeds the pressure in the brachial artery, it compresses the artery so that blood cannot flow through it and the radial pulse can no longer be palpated. When the valve of the inflation bulb is released, the bladder within the occluding cuff gradually deflates and the cuff pressure falls. When the pressure has fallen to the level of the peak pressure generated by left ventricular contraction,
blood begins to flow intermittently through the brachial artery, producing sharp, rhythmic, knocking (Korotkoff) sounds with each cardiac beat. As the cuff pressure is gradually decreased further, the sounds change in quality and intensity, may become transiently inaudible, and finally disappear when the pressure within the occluding cuff is less than the pressure in the artery throughout the full cardiac cycle. These Korotkoff sounds are described as phases:

**Phase I:** The pressure level at which the first faint, clear tapping sounds are heard. The sounds gradually increase in intensity as the cuff is deflated.

**Phase II:** That time during cuff deflation when a murmur or swishing sounds are heard.

**Phase III:** The period during which sounds are crisper and increase in intensity.

**Phase IV:** That time when a distinct, abrupt, muffling of sound (usually of a soft, blowing quality) is heard.

**Phase V:** That pressure level when the last sound is heard and after which all sound disappears.

**Systolic pressure**

The pressure at which the first sound is audible during this deflation process is the systolic pressure.

**Diastolic pressure**

The diastolic pressure is the residual pressure within the arterial tree between peaks (which represent cardiac contractions) of systolic pressure. In children, the diastolic pressure probably corresponds better with Phase IV (muffling). However, Phase V (the last audible sound) marks disappearance of sounds and probably reflects adult diastolic pressure best. (Information in this section is discussed in greater detail elsewhere in this Appendix.)

**PROCEDURES FOR INDIRECT BLOOD PRESSURE DETERMINATION BY AUSCULTATORY METHOD**

Inaccuracies of blood pressure measurement may result from defective equipment, observer error, and failure to standardize the measurement technique. Errors that result from the use of faulty measuring devices or equipment standards are discussed elsewhere in this Appendix. This section considers the person having his or her blood pressure taken, the observer, and the need for standardized techniques among observers.

**The patient** Every attempt should be made to obtain a blood pressure reading that is representative of the patient’s blood pressure under “ordinary” and reproducible circumstances. This is best accomplished when blood pressures are taken in a quiet room at a comfortable temperature after the individual has rested for 5 minutes.

The patient's arm should be bared, unrestricted by clothing, with the palm of the hand exposed upward and the elbow flexed at the heart level. Ideally, the person
should not have eaten or smoked for 30 minutes prior to the blood pressure measurement.

The presence of biological and environmental factors that affect blood pressure should be noted. These include anxiety, distention of the urinary bladder, changes or extremes in temperature, exertion, pain, and recent smoking or food intake. Over-the-counter or prescribed drugs or medications may also influence pressure measurements (6).

Observer. The importance of specialized training for lay personnel and professionals measuring blood pressure has been well established (7). The observer must be able to hear well enough to recognize faint blood pressure sounds, to see well enough to read the calibration marks on the manometer, and to coordinate eye, hand, and ear skills. Blood pressure sounds must be accurately interpreted for a correct reading. And finally, the observer must remember and record observations accurately.

The technique of blood pressure measurement has not always been taught in a standard manner, but recommendations for detection and referral have been defined more precisely over the years. Thus, previously trained individuals should periodically review the method of measuring blood pressure and correct improper habits. Standardized training for blood pressure reading should also include the most recent information on detection and referral. Techniques to assist in verifying pressure readings have been developed, including the use of a double stethoscope. Videotaped or filmed blood pressure recordings may be used to standardize techniques, to test accuracy and reproducibility, and to identify and correct observer errors. (Information about these teaching aids may be obtained either from affiliates of the American Heart Association or the National High Blood Pressure Education Program. [The National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20205]).

Although single, casual blood pressure readings may have predictive value, they do not provide an accurate assessment of an individual’s blood pressure (6, 8). Two or more blood pressure measurements from the same arm with the subject supine or seated, then standing, should be obtained at one examination. Blood pressure should then be measured in the other arm. At the initial examination, the pressure in both arms should be recorded. In subsequent examinations, blood pressure should be measured in the arm with the higher pressure on the initial examination.

The average of at least two blood pressure measurements, taken while the subject is seated, should be used to determine which individuals should be rechecked. Those with elevated blood pressures on a second occasion should be referred for treatment. At least three measurements, obtained on different days, should be obtained before an individual is classified as hypertensive. The foregoing guidelines may have to be modified, depending on the clinical circumstances.

Equipment for indirect measurement of blood pressure

Sphygmomanometer

Bladder and cuff. The inflatable bladder is surrounded by an unyielding covering
termed the cuff. A bladder that is not the appropriate width for the patient’s arm circumference will cause a systematic error in blood pressure measurement. If the bladder is too wide, the pressure will be underestimated; if the bladder is too narrow, the pressure will be overestimated. Given the same disproportion of bladder width in relation to arm circumference, the wider bladder will yield more accurate blood pressure measurements than will the narrower bladder (9, 10). The use of a narrower bladder, resulting in an overestimation of blood pressure, can lead to a false diagnosis of hypertension. This is especially true when using a regular adult cuff on obese individuals with wide arms.

The preponderance of evidence indicates that the correct ratio of bladder width to arm circumference is 0.4. Therefore, to avoid systematic error, the bladder width should be 40 to 50% of upper arm circumference (9). Expressed another way, the bladder width multiplied by 2.5 defines the ideal arm circumference for that particular cuff. For example, the ideal arm circumference for a bladder width of 12 cm is $12.0 \times 2.5 = 30$ cm. If this same 12-cm bladder is used on an individual with an upper-arm circumference that is not exactly 30 cm, a systematic error in blood pressure determination will result. The greater the deviation in the ratio of bladder width to arm circumference from 0.4, the greater will be the measurement error.

Although the American Heart Association has long advocated standardization of bladder size (4), manufacturers continue to produce cuffs of a variety of sizes. Blood pressure cuffs from different manufacturers labelled adult, large adult, or thigh may have different bladder widths despite identical labelling. This can cause further random error in serial blood pressure measurements in the same patient unless there is consistent use of the same cuff. Most adult cuffs, however, are very close to the recommended bladder length-to-width ratio of 2:1, thus ensuring that if the bladder width is 40% of arm circumference, the bladder length will encircle 80% of the arm. Several investigators have reported that bladders 35 cm long (11), or long enough to completely encircle the arm (12), yield measurements that correlate best with direct intra-arterial readings and reduced intersubject variation. Subsequent studies (13), however, have not confirmed these conclusions. A bladder length that is at least 80% of arm circumference is considered satisfactory (13). Care should be taken to center the bladder directly over the brachial artery.

Most commercial blood pressure cuffs are imprinted with a so-called ‘range’ to indicate the confidence limits for appropriate arm circumferences. Despite this range, there are problems. Some cuffs have an incorrect midpoint designated for ideal arm circumference, one that is not equal to bladder width $\times 2.5$. Additionally, some printed ranges are so broad that potentially significant errors in blood pressure measurement may result at each end of the range.

These conclusions are based on a large study undertaken to calculate the expected error of blood pressure measurements from the most widely used adult cuffs in relation to arm circumference (10). Corrected systolic and diastolic pressure readings were obtained with different cuff sizes at various arm circumferences. Table 1 reflects data collected for the most commonly used adult bladder widths: 12 cm (adult), 15 cm (large), and 18 cm (thigh). A difference in bladder width of 1.0 cm does not appreciably alter the corrections. Similar data for other bladder sizes are not available.

When highly accurate blood pressure measurements are necessary for research
studies, arm circumferences should be measured and corrections made from Table 1. For routine blood pressure measurements by health-care providers, the following guidelines are recommended:

Marking each cuff  (1) If the manufacturer provides the width of the inflatable bladder in centimeters, mark this measurement with indelible ink on the cuff. If not, measure the width of the inflatable bladder in centimeters. (Do not measure the cuff width, which is wider.) Mark this measurement on the cuff in indelible ink for future reference. (2) Multiply the bladder width in centimeters by 2.5. This calculation is the correct arm circumference for the bladder. Measuring distally from the index line of the cuff, mark this distance with a line, which indicates the ideal arm circumference.

Selection of cuff size  A cuff that is too wide causes less error than one that is too narrow. It is recommended that the large cuff (15 cm) be used for all adults except those with thin arms that are out of the cuff range. Blood pressure may be slightly underestimated in those with arm circumferences of less than 33 cm. Thigh cuffs should be used for obese individuals whose arm circumferences are greater than 41 cm.

| Table 1  Recommended ideal arm circumference, arm circumference ranges, and correction of systolic and diastolic readings for adult blood pressure cuffs of different bladder widths at various arm circumferences (3) |
|-----------------|---------|---------|---------|
| Bladder width (cm) | 12      | 15      | 18      |
| Ideal arm circumference (cm) | 30.0    | 37.5    | 45.0    |
| Arm circumference range (cm) | 26–33   | 33–41   | > 41    |

<table>
<thead>
<tr>
<th>Arm circumference (cm)</th>
<th>SBP</th>
<th>DBP</th>
<th>SBP</th>
<th>DBP</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>+5</td>
<td>+3</td>
<td>+7</td>
<td>+5</td>
<td>+9</td>
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<td>30</td>
<td>0</td>
<td>+4</td>
<td>+3</td>
<td>+7</td>
<td>+4</td>
<td></td>
</tr>
<tr>
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<td>-2</td>
<td>-1</td>
<td>+3</td>
<td>+2</td>
<td>+6</td>
<td>+4</td>
</tr>
<tr>
<td>34</td>
<td>-4</td>
<td>-2</td>
<td>+1</td>
<td>+5</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>-6</td>
<td>-4</td>
<td>0</td>
<td>+1</td>
<td>+5</td>
<td>+3</td>
</tr>
<tr>
<td>38</td>
<td>-8</td>
<td>-6</td>
<td>-1</td>
<td>0</td>
<td>+4</td>
<td>+2</td>
</tr>
<tr>
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<td>-10</td>
<td>-7</td>
<td>-2</td>
<td>-1</td>
<td>+3</td>
<td>+1</td>
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<td>-9</td>
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<td>+1</td>
</tr>
<tr>
<td>44</td>
<td>-14</td>
<td>-10</td>
<td>-5</td>
<td>-3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>46</td>
<td>-16</td>
<td>-11</td>
<td>-6</td>
<td>-3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>48</td>
<td>-18</td>
<td>-13</td>
<td>-7</td>
<td>-4</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>50</td>
<td>-21</td>
<td>-14</td>
<td>-9</td>
<td>-5</td>
<td>-1</td>
<td>-1</td>
</tr>
</tbody>
</table>

For correction of blood pressure readings in individual patients, positive numbers should be added to and negative numbers subtracted from the readings obtained. SBP = systolic correction in millimeters of mercury; DBP = diastolic correction in millimeters of mercury.
A cuff error of only a few millimeters of mercury may cause a patient to be misclassified as either normotensive or hypertensive (10). When initial diastolic pressures are between 85 mmHg (high normal) (6) and 100 mmHg, upper-arm circumference should be measured and appropriate corrections made (Table 1). Arm circumference need be measured only initially for each patient unless there is significant change in weight.

If the average diastolic pressure is less than 85 mmHg from several readings, it may be assumed that the patient is not hypertensive. If the diastolic pressure is 90 mmHg or greater on at least three separate occasions, the patient is hypertensive.

Manometers The mercury gravity manometer and the aneroid manometer are the two pressure-registering systems in general use. Both give accurate and reproducible results when functioning properly. (For more detailed information, refer to publications on automated and nonautomated sphygmomanometers available from the Association for the Advancement of Medical Instrumentation, 1901 Fort Meyer Drive, Suite 602, Arlington, VA 22209-1699.)

Mercury manometers Care should be taken when using the mercury manometer to avoid loss of mercury. The level of mercury in the column should be observed without applying pressure to the cuff. If necessary, mercury can be added to the reservoir in order to bring the edge of the meniscus precisely to the zero mark. The scale should accurately indicate differences between the levels of mercury in the column and the reservoir. To accomplish this, the diameter of the reservoir must be at least ten times that of the vertical column, or the vertical scale must be calibrated to correct for the drop in the mercury level in the reservoir as the level in the column rises. The column of the usual desk or wall manometer must be vertical for a correct reading although some mobile or floor-based mercury manometers are designed to be read at a reclined angle and the gradations are adjusted accordingly. It is important that the instrument be used with the column and its scale in the correct position. The column of the mercury manometer should be inspected regularly for dirt and signs of oxidation. A clogged air vent or filter at the top of the manometer column will cause the mercury to respond sluggishly to declining pressure in the bladder and cause an erroneous measurement. The filter and the vent should be serviced at least once annually to ensure continued accuracy. Mercury that does not rise easily or that bounces noticeably when the valve is closed indicates that the pores in the kid-skin diaphragm are clogged.

Aneroid manometers Aneroid manometers use metal bellows that expand with the application of pressure. A mechanical amplifier transmits this motion to the indicator needle. The aneroid apparatus should be calibrated at least once every 6 months with a mercury gravity manometer or other pressure standard. The examination should be made at several points over the entire pressure range since no single correspondence of readings guarantees accuracy over the range of pressures. Readings should be taken on a falling pressure to accurately typify the clinical conditions of use. Such calibration is done by interposing a Y connector in the tube from the cuff to a mercury manometer and attaching the aneroid manometer to be tested to the free end of the connector. Not recommended are aneroid manometers with a stop pin at zero, a rotatable dial, or an external reset that permits adjustment of the zero mark to any angle on the face since a satisfactory check of the accuracy
of such manometers is impossible.

Electronic manometers A large number of electronic manometers has been introduced recently. Most are used by individuals for home blood pressure determinations. It is almost impossible to assess the accuracy of these instruments. However, a statement on the use of these and other indirect blood pressure recording devices has been published by the Joint Coordination Committee of the High Blood Pressure Education Program and approved by the AHA (14). Electronic equipment is not generally used by health-care providers. It is recommended that these devices be checked frequently and standardized against a mercury manometer.

Errors in blood pressure readings can also be caused by variations of microphone sensitivity in identifying Korotkoff sounds. Microphone sensitivity can be affected by incorrect positioning of the cuff of arm, movement, friction, ambient noise, or mechanical or electric damage (Table 2).

Inflating system, exhaust valve, and tubing Elements of the sphygmomanometer should be checked frequently for significant leaks in pressure (i.e., more than 1 mmHg/sec) and for competent, smooth functioning of the input system and the bulb exhaust valves. The system should be capable of gradual or rapid inflation. Another potential source of error is malfunction of the pump system, which leads to occluding pressures that are too high, too low, or that deflate improperly (Table 3).

<table>
<thead>
<tr>
<th>TABLE 2 Causes of artifacts in blood pressure measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artifacts due to equipment</strong></td>
</tr>
<tr>
<td>Inadequately tested or calibrated systems</td>
</tr>
<tr>
<td>Mercury/gravity or aneroid sphygmomanometer defects: clogged air vent; improper calibration; incompletely deflated bladder; faulty tubing, inflation system, or exhaust valve; insufficient mercury in reservoir; failure to ‘zero’ indicator</td>
</tr>
<tr>
<td>Cuff size/arm size disparity. Limb circumference-to-cuff width ratio of greater or less than 2.5 produces falsely high or low indirect pressure readings, respectively</td>
</tr>
<tr>
<td><strong>Artifacts due to examiner technique</strong></td>
</tr>
<tr>
<td>Unsupported arm gives falsely higher pressure</td>
</tr>
<tr>
<td>Examiner positions instrument at level above or below heart or presses stethoscope too firmly over vessel.</td>
</tr>
<tr>
<td>Examiner has preference for even-numbered digits, etc.</td>
</tr>
<tr>
<td>Cold hands of examiner or cold equipment raises blood pressure</td>
</tr>
<tr>
<td>Subject—examiner interaction affects pressure reading</td>
</tr>
<tr>
<td>Acoustic monitoring system is impaired</td>
</tr>
<tr>
<td>Source</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Instrument</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Bladder</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Cuff</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Tubing</td>
</tr>
<tr>
<td>Stethoscope</td>
</tr>
<tr>
<td>Sensory impairment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Stethoscope</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Deflation rate</td>
</tr>
</tbody>
</table>

(continued)
TABLE 3  (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Cause</th>
<th>Effect</th>
<th>Method to reduce</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflating cuff</td>
<td>Excessive and unnecessary high pressure</td>
<td>Painful to patient and may result in falsely high reading</td>
<td>Determine maximum inflation level</td>
</tr>
<tr>
<td></td>
<td>Maximum inflation level not determined</td>
<td>May mistake onset of Phase III for onset of Phase I</td>
<td>Preliminary palpation for systolic pressure — maximum inflation level</td>
</tr>
<tr>
<td>Subconscious bias</td>
<td>Digit preference</td>
<td>Improper reading is recorded</td>
<td>Read mercury column accurately</td>
</tr>
<tr>
<td>Systolic recheck</td>
<td>System initiated after deflation has begun</td>
<td>Blood trapped in forearm; inaccurate reading</td>
<td>To recheck systolic pressure, completely deflate system, wait 1 – 2 minutes begin again</td>
</tr>
</tbody>
</table>

* Adapted from Russell HP, Lewis C, Fedder DD: Sphygmomanometry: Time to put the science back into the art. MD State Med J 1984; 33: 879 – 881. Used by permission. (Originally adapted from Chicago Heart Association: Manual for instructors in the measurement of blood pressure, July 1976.)

**Stethoscope**

The stethoscope should be of a standard variety and in good condition. Because sound generated over the vessels is relatively low in frequency, the bell head (or its equivalent) should be used to measure blood pressure.

**Techniques**

Two methods are recommended for intensifying the Korotkoff sounds:

- Elevate the subject’s arm before and during inflation, and then lower the arm after the cuff has been inflated. Blood pressure is then determined in the usual manner.
- Inflate the cuff, and then have the subject open and close his fist several times before determining the blood pressure.

**Recording blood pressure**

The observer should note the person’s position (1. sitting or supine and 2. standing), the cuff size (pediatric, wide, or thigh cuff), and the arm used. It is also important to describe and record whether an irregular pulse or auscultatory gap was present.

The accuracy and reliability of blood pressure readings will increase by following these standardized steps:
1. Situate the individual in a quiet environment with the arm resting at heart level. Put him/her at ease and allow a 5-minute rest.

2. Place the manometer at eye level, sufficiently close to read the calibrations marking the gauge or column.

3. Select the appropriately sized cuff. Bladder width should be at least 40% of arm circumference; bladder length should be at least 80% of arm circumference (6, 9-13, 15).

4. Locate the brachial artery along the inner upper arm by palpation.

5. Wrap the cuff smoothly and snugly around the arm, centering the bladder over the brachial artery. The lower margin should be 2.5 cm above the antecubital space. (Do not rely on cuff marking; find the center by folding the bladder in half.)

6. Determine the level for maximal inflation by observing the pressure at which the radial pulse is no longer palpable as the cuff is rapidly inflated (palpated systolic) and by adding 30 mmHg. (Note the presence of an irregular pulse.)

7. Rapidly and steadily deflate the cuff. Then wait 15 to 30 seconds before reinflating.

8. Position the stethoscope over the palpated brachial artery below the cuff at the antecubital fossa. Ear pieces should point forward. The bell head of the stethoscope should be applied with light pressure, ensuring skin contact at all points. Heavy pressure may distort sounds.

9. Rapidly and steadily inflate the cuff to the maximal inflation level as determined in Step 6.

10. Release the air in the cuff so that the pressure falls at a rate of 2 to 3 mm per second.

11. Note the systolic pressure at the onset of at least two consecutive beats (Phase I) for both adults and children. Blood pressure levels should always be recorded in even numbers and read to the nearest 2 mmHg mark on the manometer.

12. Note the diastolic pressure at muffing (Phase IV) for children and cessation of sound (Phase V) for adults. Phase V, at which the last sound is heard, is the diastolic pressure in adults. Listen for 10 to 20 mmHg below the last sound heard to confirm disappearance, and then deflate the cuff rapidly and completely.

13. Record systolic/diastolic pressure. When the pressure at Phase IV is recorded, the pressure at Phase V should also be recorded. Example: 108/64/52 or 110/66/0 mmHg.

14. Record the patient's position, cuff size, and the arm used for the measurement.

15. Wait 1 to 2 minutes before repeating the pressure measurement in the same arm to permit the release of blood trapped in the arm veins.

**Special pitfalls and problems**

*Absent Phase V*

In certain patients, the Korotkoff sounds do not disappear, but may be heard until the pressure in the cuff falls to near 0 mmHg. This is often the case in children, patients with aortic valvular insufficiency, or high cardiac output (as in anemia,
thyrotoxicosis, or pregnancy), and in patients with marked vasodilatation (e.g., after exercising). Under these conditions, Phase IV, during which the pitch of the Korotkoff sounds changes, is a more reliable index of diastolic blood pressure than is Phase V. When indirect blood pressure determinations are compared simultaneously with intra-arterial blood pressure measurements, there is a fair correlation on the average, but wide disparities to +18 or -30 mmHg have been reported for both systolic and diastolic pressure as measured by the indirect technique. In any event, if sounds are heard to zero, both Phases IV and V should be recorded (i.e., 148/72/0 mmHg).

The auscultatory gap

In some subjects, particularly in patients with hypertension, the sounds heard over the brachial artery when the cuff pressure is high disappear as the pressure is reduced and then reappear at some lower level. This early, temporary disappearance of sound is called the auscultatory gap and occurs during the latter part of Phase I and Phase II. Because this gap may extend over a range as great as 40 mmHg, one may seriously underestimate the systolic pressure or overestimate the diastolic pressure, unless its presence is excluded by first palpating for disappearance of the radial pulse as the cuff pressure is raised.

Effect of arm position

The pressure in the arm increases as the arm is lowered from the level of the heart (phlebostatic axis); conversely, raising the arm above this position lowers the pressure measurement. The effect is largely explained by hydrostatic pressure or by the effect of gravity on the column of blood. Therefore, when measuring indirect blood pressure, the patient’s arm should be positioned so that the location of the stethoscope head (preferably, the bell or its equivalent) is at the level of the heart. This location of the heart is arbitrarily taken to be at the junction of the fourth intercostal space and the lower left sternal border. Attention to the position of the brachial artery in relation to the heart is particularly important when the patient is standing upright. No corrections for position need to be made if the patient is lying supine on a flat surface with the head slightly raised, since the arm by the side of the body is sufficiently close to the level of the heart. When the patient is seated, placing the arm on a nearby tabletop a little above waist level will result in a satisfactory position. If the position of the arm cannot be appropriately adjusted, a correction for the hydrostatic pressure must be made: For each 1 cm of vertical height above or below the heart level, 0.8 mmHg must be added or subtracted, respectively, to the observed pressure.

Positioning the manometer at the level of the heart is not necessary, but it must be clearly visible to the observer. Ideally, the mercury manometer should be at eye level so that the mercury meniscus can be easily read without parallax (Table 3).

Cardiac dysrhythmias

If the cardiac rhythm is irregular, accurate determination of blood pressure by
sphygmomanometry may be difficult because both stroke volume and blood pressure may be highly variable from one cardiac cycle to the next. Systolic pressure is directly related to the duration of the preceding pulse cycle and the stroke volume. Moreover, pulse pressure is related inversely to the duration of the pulse cycle; a long pulse cycle results in a decreased diastolic pressure of that cycle and an increased systolic pressure of the following cycle.

An occasional premature cardiac contraction may be ignored, but repeated measurements are important when they occur frequently, consecutively, or when atrial fibrillation is present. Under these circumstances, both systolic and diastolic pressure readings should be recorded only as an approximation, and the presence and nature of the cardiac dysrhythmia should be recorded together with the blood pressure and the heart rate (apical and peripheral). For patients with atrial fibrillation, the systolic pressure should be recorded as the average of a series of Phase I readings, and diastolic pressure should be recorded as an average of Phases IV and V.

**Blood pressure in thigh, leg, and forearm**

Blood pressure in the thigh is measured with the largest available cuff and bladder (Table 4). With the patient lying face down, the cuff is applied so that the inflation bladder is over the posterior aspect of the midthigh. The stethoscope is placed over the artery at the popliteal fossa, and the Korotkoff sounds are monitored as cuff pressure is lowered, in the same manner as in the arms. If the patient is unable to lie face down, thigh blood pressure may be obtained with the patient lying on his/her back with the knee of the leg to be measured slightly flexed, enough to permit application of the stethoscope over the popliteal space. The diastolic pressure in the legs is usually similar to that in the arms, but the systolic pressure may be 20–30 mm higher than in the arms. Systolic pressure may be approximated in the lower leg by palpation of the pulses over the posterior tibial or dorsalis pedis arteries. The pressures in the lower leg are similar to those in the thigh. The cuff

<table>
<thead>
<tr>
<th>Arm circumference at midpoint* (cm)</th>
<th>Cuff name</th>
<th>Bladder width (cm)</th>
<th>Bladder length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 7.5</td>
<td>Newborn</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>7.5 - 13</td>
<td>Infant</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>13 - 20</td>
<td>Child</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>24 - 32</td>
<td>Adult</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>32 - 42</td>
<td>Wide adult</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>42 - 50'</td>
<td>Thigh</td>
<td>20</td>
<td>42</td>
</tr>
</tbody>
</table>

* Midpoint of arm is defined as half the distance from acromion to olecranon. Use nonstretchable metal tape.

† In persons with very large limbs, indirect blood pressure should be measured in leg of forearm.
is applied over the lower leg with the distal border of the cuff at the malleoli.

Occasionally, in patients with very large upper arms, pressure may be measured in the forearm if a large adult cuff is not available. The radial artery is used as the site for monitoring. These measurements are not usually performed since falsely higher diastolic readings may be obtained; their relation to intra-arterial pressure has not been clearly defined.

In patients with occlusive peripheral vascular disease, pressures may be unobtainable in the lower extremities. Pressures measured in both arms are usually within a few millimeters of mercury of each other unless occlusive vascular disease is present.

When the arms or thighs are so large or misshapen that conventional cuffs cannot be properly applied, accurate indirect blood pressure measurements cannot be made. In these situations, intra-arterial blood pressure measurements may be necessary.

**Clinical shock**

Brachial arterial pulsations and Korotkoff sounds may be diminished or absent in clinical shock. In patients who are in circulatory shock, comparisons between auscultatory pressures and direct arterial readings taken with a needle inserted into the femoral artery frequently reveal that the direct femoral pressure is considerably higher than the pressure recorded in the arm by the auscultatory method (16). Diminution or disappearance of Korotkoff sounds is frequently obtained in shock states associated with greatly reduced cardiac output and elevated total peripheral resistance. Because of high vascular resistance in the forearm, blood flow in the extremities may fall to such low levels that the Korotkoff sounds are markedly diminished or inaudible. Under this circumstance, ultrasound methods, such as the Doppler technique, may provide more reliable indirect blood pressure measurements in hypotensive (shock) states (17). In these critically ill patients, however, direct measurement and recording of arterial pressure may be necessary for adequate clinical management.

**Obesity**

Although obese patients have a higher prevalence of hypertension, falsely elevated indirect pressure measurements may be obtained in patients with increased arm girth if the standard-sized bladder and technique are used (10). This is caused by the use of bladders that are too small, with subsequent excessive loss of cuff pressure through the thick, compressible soft tissues of obese arms. This problem may be minimized by using a bladder width that is 40 to 50% of measured arm circumference.

In moderately obese individuals, a large adult cuff (15 cm wide) will usually be adequate. In morbidly obese individuals (arm circumference greater than 41 cm), a thigh cuff (18 cm wide) should be used. In individuals with short, wide arms, if the thigh cuff is too long, a large adult cuff may be used, and the measured blood pressure can be corrected by reference to Table 1.

Forearm blood pressure determination is not recommended because of falsely
higher diastolic readings when compared with upper arm measurement using the proper sized cuff.

*Pseudohypertension*

In older patients who have sclerotic or calcified vessels, the stiff, thick, hard vessel wall may resist compression by the inflation bladder. Thus, more pressure may be needed to occlude the artery, resulting in a spuriously high estimation of systolic pressure (18). This condition may be recognized clinically when the radial or brachial artery is easily palpable even when the cuff is inflated above systolic blood pressure so that the artery is not filled with blood.

**EPIDEMIOLOGIC METHODS**

Blood pressure measurements are often obtained in epidemiological studies designed to answer a variety of questions concerning blood pressure values in populations. Estimates of the prevalence of high blood pressure, descriptive patterns of blood pressure values in specific groups, the prediction of blood pressure changes in a study population, and the evaluation of antihypertensive therapy are examples of such questions. Concern for the validity of these types of epidemiologic studies and the need to compare results across multiple investigations lends special importance to considerations of reliability and comparability of blood pressure measurements.

The potential sources of error and systematic differences in measurement technique in epidemiologic studies have received much attention. True variation of blood pressure in the individual study participant can be controlled to a satisfactory degree by maintenance of appropriate ambient conditions in the measurement situation. The relevant issues here are posture, arm position, resting state, and others that were discussed earlier. For children, special requirements are discussed in the section on ‘Determination of Blood Pressure in Infants, Children, and Adolescents.’

Measurement error is controlled by attention to both the equipment in use and the observer. Aspects of the choice of equipment have been addressed earlier. It should be emphasized that devices aimed at reduction of measurement error through lesser dependence on the skills of the observer are increasingly available but generally require careful experimental evaluation before adoption in place of the standard technique (19). Another area in which newer technical advancements are occurring is in the development of devices for continuous indirect blood pressure monitoring; the current literature should be consulted when considering their use.

The remaining source of error is the observer, whose skill or lack thereof can be decisive in the acceptability of measurements. With the standard technique described earlier, the observer must correctly perform the following steps:

- Judge the preparedness of the subject and equipment and the suitability of the circumstance of measurement.
- Position the subject, equipment, and the observer appropriately.
- Select and place the cuff correctly.
- Estimate the maximum inflation pressure.
• Inflate the cuff to correct pressure.
• Control the deflation rate while concentrating on the appearance, quality, and disappearance of the Korotkoff sounds.
• Note and retain mentally the corresponding pressure values.
• Record the values observed.

In addition to learning correct procedure, the observer must overcome unconscious biases when reading the manometer scale. First, the design of the scale leads to a tendency to read zero-ending values and digit preference. Thus, many persons tend to favor the choice of one digit over another in reading measurement scales. This source of error can be eliminated by making the observer aware of this tendency. Further, knowledge of the blood pressure criteria for making decisions about screening, referral, or treatment decisions can influence the observer’s judgment when the reading appears to be near such values. These sources of error are most effectively controlled by devices that ‘blind’ the observer to the actual pressure values until after the reading has been completed (e.g., the Hawksley Random-Zero Device and the London School of Hygiene sphygmomanometer (15, 20)).

Correction of other sources of error depends on training that addresses each step of the measurement procedure. Some programs permit quantitative assessment of the performance of each trainee in comparison with the standard reading from film or videotape sequences of actual readings.

The clinical implications of blood pressure measurement make accuracy of this aspect of physical examination as important as any other diagnostic procedure. It would be desirable for standards of clinical sphygmomanometry to approach those used in research.

**HOME, SELF-MONITORED, AND AMBULATORY BLOOD PRESSURE MEASUREMENTS**

Home blood pressure measurements have been used with increasing frequency to:

• Determine blood pressure levels away from the physician’s office or clinic setting.
• Obviate frequent visits to physicians or clinics.
• Establish a baseline before initiating therapy.
• Assess the effectiveness and need for titration of medication.
• Help the patient become more aware of his/her blood pressure level; this can promote understanding and active participation in the management of hypertension and improve adherence to therapy since self-monitoring provides a ready feedback.

Some patients welcome the opportunity to participate in their own management, whereas others become alarmed by minor changes in pressure. The average of multiple home recordings is more likely to reflect the true average of an individual’s prevailing pressure than are formal office or clinic measurements. However, to confirm the reliability of home measurements, the health provider should check the
patient’s pressure measurements and equipment using a ‘double stethoscope’ with a tube connecting the two instruments.

Some home blood pressure measurement instruments are very easy to use. They have a specially designed cuff with a built-in microphone and straps that permit one-handed attachment and comfortable fitting of the cuff on the non-dominant arm. The tubing from the cuff to inflation bulb and to manometer must be sufficiently long for comfortable positioning of the patient and for the observer to inflate the bulb with the dominant hand and reading the blood pressure level. Contortions of the body and angled viewing of the manometer can result in faulty determinations.

Numerous instruments for self-monitored blood pressure measurements have become available in recent years. A mercury manometer or aneroid manometer can be readily checked and calibrated against the physician’s standard office manometer and should be done periodically. However, the more complicated machines that provide only a digital read-out of systolic and diastolic pressure and pulse cannot be checked readily for accuracy in the office. Because of the relatively slow rate of deflation, especially in patients with high systolic pressures, spuriously high diastolic pressure levels are often recorded. Whatever the equipment selected, however, the patient should ensure that there is ready access to regular servicing, calibration, repair, and quality control of the machine purchased, or knowledge on how to obtain them.

It is important to realize that, under normal circumstances, blood pressure fluctuates constantly in response to multiple factors such as mental or muscular activity, body position, pain, temperature, etc. With the use of techniques for measuring blood pressure automatically, either continuously or intermittently over 12 to 24 hours in ambulatory patients, the extent of these fluctuations has become more widely recognized. Therefore, it is possible that the few measurements made in the physician’s office or clinic may not be representative of the average blood pressure or even the range of fluctuations over time. Furthermore, many patients respond to the clinical or office setting with a rise in pressure, which may or may not lessen in intensity with repeated visits and can give a misleading picture of the patient’s normal blood pressure.

The available methods for ambulatory blood pressure measurements (repeated readings in patients going about their normal activities) are expensive, time-consuming, and require a specialized laboratory and equipment for analysis. They are currently not practical for widespread and general clinical application. Moreover, data are not yet available concerning ‘normal’ ambulatory 24-hour home pressures. However, these techniques may be useful in selected patients whose office blood pressure measurements do not correlate with the severity or lack of end-organ damage; whose symptoms suggest episodes of excessive rise or fall of blood pressure (e.g., pheochromocytoma); whose pressures are extremely labile or borderline elevated, making the decision for treatment difficult; or whose symptoms may be correlated with blood pressure elevation (e.g., angina pectoris). These techniques may also be useful for investigative purposes.
DETERMINATION OF BLOOD PRESSURE IN INFANTS, CHILDREN, AND ADOLESCENTS

Blood pressure can be determined accurately by the auscultatory method in children, providing attention is paid to the following:

- Readings are difficult to obtain and interpret in anxious or restless children.
- Cuffs must be of appropriate sizes for various arm sizes. An inappropriately narrow cuff will result in overestimation of blood pressure.
- Korotkoff-like sounds are easily generated by excessive stethoscope pressure over the brachial artery and may cause errors in measurement.

Direct measurements of blood pressure in children indicate that the criteria for adult cuff sizes are also optimal for children; that is, the bladder width should be 40% of arm circumference (21). The bladder should completely or nearly completely encircle the extremity without overlap. Cuffs are labeled as newborn, infant, child, small adult, and large adult. Cuff size should be appropriate for the size of the arm and should not be selected on the basis of age. If the choice lies between choosing a cuff that is slightly narrow for the arm or one that is a little wide, the latter should be used as long as the axilla and antecubital fossa are not obstructed.

The child should be in a comfortable position with the arm fully exposed and resting on a supporting surface at heart level. Care should be taken that all extremities are relaxed. Infants should be supine and children seated for the measurement. The examining area should be quiet and the child reassured. Sufficient time should be allowed for recovery from recent activity, apprehension, or crying.

The technique for obtaining blood pressure is identical to that described for adults. In children, the Korotkoff sounds in Phase IV best represent the measure of diastolic pressure since disappearance of sound may not occur. Both Phases IV and V should be recorded. In adolescents, the interpretation of the Korotkoff sounds is similar to that in adults, and the sounds in Phase V best represent diastolic blood pressure. In infants, the auscultatory sounds are difficult to hear, and an ultrasonic method is recommended. Ultrasound has been found to provide accurate measurements of systolic, but not of diastolic, pressure in infants (22–24). Wide cuff bladders (50% or greater of arm circumference) have been found to give better approximations of intra-arterial blood pressure than narrower bladders when Doppler sensing devices are used (25, 26). When wide bladders are used for ultrasonic measurement of systolic pressure, falsely low blood pressures are not observed, as has been reported when wide bladders have been used with auscultatory techniques (10). Prior to measuring blood pressure, the infant should be quieted either by feeding or using a pacifier.

Because of the possible lability of blood pressure in children, a single elevated measurement may not be representative of the usual pressure. Children whose first measurement is elevated should have the blood pressure remeasured at least three times on different occasions before a diagnosis of hypertension is established.

Blood pressure levels in normal children are dependent on body height and lean body mass as well as age; blood pressure normally increases with increasing age.
and/or body size (27). Both variables must be considered when interpreting blood pressure measurements in children and adolescents — a blood pressure high for age may be normal if the patient is tall or has increased lean body mass for age.

The following definitions of blood pressure classification (28) may be used in children:

*Normal blood pressure:* Systolic and diastolic pressure is less than the 90th percentile for age and sex.

*High normal blood pressure:* Systolic and/or diastolic blood pressure is between the 90th and 95th percentiles for age and sex. (If pressure is high normal for age, but can be accounted for by excess height for age or excess lean body mass, blood pressure is considered normal.)

*High blood pressure:* Systolic and/or diastolic pressure equal to or greater than the 95th percentile for age and sex, as measured on at least three occasions.

**APPENDIX**

**Notes concerning criteria for diastolic pressure**

The Task Force recommends, based on factors discussed below, that for the diastolic pressure in adults one should use Phase V and in children, Phase IV Korotkoff sounds. Both Phases IV and V sounds should be recorded if they are different. In adolescents, Phase V sounds best represent diastolic pressure. In infants, ultra-sounds provide accurate measurements of systolic but not of diastolic pressure.

Each committee that has revised *Recommendations for Human Blood Pressure Determination by Sphygmomanometer* has considered the recommendations of its predecessors. Concepts have changed about the criteria for diastolic pressure. The original joint statement, in 1939, of the American Heart Association and the Cardiac Society of Great Britain and Ireland recommended that Korotkoff sounds in Phase IV (muffling) be adopted as the criterion for diastolic blood pressure. In 1951, however, a second committee, chaired by Dr. Carl Wiggers, recommended that Phase IV be replaced by Phase V (disappearance of sounds) as the best indication in adults.

In 1967, a third committee was appointed to review the previous recommendations. This committee was concerned with hydrodynamic considerations associated with the effects of cuff deflation on the compressed brachial artery segment. During Phase III, snapping sounds are associated with an abrupt opening of the compressed arterial segment during each pulse cycle. When the cuff pressure falls below diastolic pressure, the artery remains open throughout the pulse cycle so that staccato sounds are no longer generated. The committee recommended that both Phases IV and V be reported but that Phase IV was the better index of diastolic pressure.

The hemodynamic considerations described above, while valid, fail to take into account the loss of pressure energy that occurs when the brachial artery is compressed by an external cuff. The original hemodynamic observations considered by the committee were made in the exposed dog femoral artery (29), where an arterial segment was enclosed within a glass chamber and air pressure was applied directly to the artery. These conditions differ markedly from the procedures used in measuring blood pressure by the indirect auscultatory method in man. Unlike the sealed chamber, the external cuff used clinically produces a loss of transmitted pressure both above and below the cuff. Further, a thick layer of soft tissue,
which is interposed between the cuff and the artery, dampens and absorbs some of the pressure. The extent of loss of cuff pressure in transmission through the soft tissue of the arm varies with several factors, the most important of which is arm circumference — the greater the intervening layer of soft tissue, the greater the loss in transmitted pressure and vice versa. With a standard arm cuff placed on an arm of average girth, the transmitted pressure loss has been measured directly and approximates 5 to 10 mmHg (30). Thus, when the pressure in the cuff at Phase IV is 80 mmHg, the pressure compressing the artery is approximately 70—75 mmHg. Hence, when Phase IV is used as the criterion of diastolic blood pressure, the reading will average 5 to 10 mmHg higher than the actual diastolic pressure.

The 1967 committee report indicated another reason for using Phase IV for measuring diastolic pressure. Phase IV indicates a change in sound quality while Phase V indicates disappearance of sound. Because Phase V employs intensity of sound, the end-point depends on such variables as position of the stethoscope over the artery, efficiency of the stethoscope in transmitting sounds of low intensity, and acuity of the observer’s hearing. Since muffling represents a change in quality of sound, it was believed to be less affected by efficiency of detection.

Another advantage stated by the 1967 committee for recommending Phase IV was that with high brachial artery flow rates (occurring during or immediately following exercise, in hyperthyroidism, or in normal infants and children), sounds may be detected below muffling for a much longer interval than is the case with normal or reduced flow rates. Under these conditions, a Phase V reading will underestimate diastolic pressure. Accordingly, in special conditions where Phase V provides a falsely low value for diastolic pressures, such as in hyperthyroidism, aortic insufficiency, exercise, or in children and infants, Phase IV should be used. This recommendation is relevant to the measurement of blood pressure during and after graded exercise testing.

In clinical practice, however, Phase IV is not always clearly defined. Frequently, the observer has more difficulty recognizing the muffling in Phase IV than recognizing the disappearance of sounds in Phase V. This is of major importance in training personnel to record blood pressure: there are greater errors in the identification of Phase IV than of Phase V (31). Also to be considered is the vast body of epidemiologic data that relates levels of diastolic pressure to increased risk of major cardiovascular complications; these data are based almost exclusively on Phase V readings. Finally, the major therapeutic intervention trials conducted in the United States and throughout the world have used Phase V as the criterion for pressure determination. For these compelling reasons, the present committee recommends the use of Phase V of the Korotkoff sound in adults (with the exceptions as noted above and in children).

Use of the International System of Units for blood pressure measurement

Certain international organizations support adopting international units to replace the conventional metric system in medicine. The Système International (SI) d’Unités was adopted at the General Conference on Weights and Measures in 1971 to provide an orderly arrangement of values to replace the variety of units presently employed. Despite its potential appeal, the system has not been widely accepted in the United States.

Several nations and scientific journals have either begun or expressed intention to use the SI units. This has been more widespread for chemical indexes than for pressure. In the SI system, the basic unit for pressure is the newton per square meter, known as the pascal (Pa): 1 mmHg = 133.32 Pa. Hence, a blood pressure of 130/97/90 becomes 17.3 kPa/13.0 kPa/12.0 kPa (k = kilo). In 1973, the International Organization of Legal Metrology 38 recommended that the unit of blood pressure measurement be the millibar (mbar): 1 mmHg = 1.33 mbar; 1 mbar = 1 hPa (hectopascal).
Notwithstanding, the committee continues to recommend that the standard unit of pressure be maintained as millimeters of mercury and the SI unit not be adopted. This opinion acknowledges that the millimeters of mercury unit expresses a quantity in terms of the manner in which the measurement is made. Moreover, there continues to be sufficient worldwide opposition to the use of the SI unit because of its awkwardness in relation to blood pressure measurement, the expense of the change, and the confusion that would certainly ensue among medical personnel were a recommendation be made to change units. Despite this recommendation to maintain the millimeters of mercury measurement, it is appropriate to be able to convert millimeters of mercury measurement into kilopascals to understand certain applications in current literature.

(A simple method of calculation to obtain millimeters of mercury from kilopascals is to multiply kPa by 7.5. Conversely, measurements made in millimeters of mercury may be transposed to kPa by dividing by 7.5.)

REFERENCES


APPENDIX IV

World Hypertension League recommendations on self-measurement of blood pressure

Although experience is still limited and more research is needed, the World Hypertension League recommends self-measurement of blood pressure in selected patients as an additional source of information to the practising physician, and as a way of encouraging patients to participate more actively in the therapeutic regimen.

Self-measurement of blood pressure — readings taken by lay persons on themselves or on a member of their family — is known to be spreading rapidly in a number of countries. Statements on the appropriate uses of such measurements have therefore been published by national bodies for hypertension control, such as the U.S. National High Blood Pressure Educations Program (1) and the German League against Hypertension (2). An increasing variety of instruments are being designed and marketed for self-measurement and people are now more exposed to publicity on these devices than even in the recent past.

The adoption of self-measurement depends to a great extent on social, cultural, economic, and medical factors. Purchasing an instrument is outside the reach of most patients in a developing country; in some societies, the act of self-measurement may be unacceptable to the majority of the public, or to the majority of physicians. Nevertheless, in view of the increasing use of self-measurement and of the potential benefits for patients, the Council of the World Hypertension League felt that an analysis of the problem and a statement on the subject would be of benefit for present and future activities to control hypertension.

ADVANTAGES AND PROBLEMS

Physiological background: the value of home measurements

Blood pressure is inherently variable and the first observations of measurement through a 24-hour period showed wide fluctuations of the order of 50/20 mmHg.

This variability was subsequently confirmed by intra-arterial readings during 24 hours (4–6), which showed that blood pressure changes rapidly with physical and mental activity (7) and falls substantially during sleep (4, 8). In addition to this spontaneous variability in pressure, the blood pressure in many subjects rises when they are in a doctor's office or clinic. For example, in a recent study it was shown that when a physician measured the blood pressure, the average rise in systolic and diastolic pressures was 14 mmHg and 7 mmHg, respectively; there was very wide individual scatter, though some patients may have lower clinic than home readings (9). In a particular subject, therefore, the unpredictable rise in blood pressure in the doctor's clinic may present problems for both the diagnosis and the treatment of hypertension. Thus, it may be useful to complement clinic readings with home measurements.

The 'alerting response' induced by a clinic visit wanes after repeated measurements and this is one reason for the well-known decline in blood pressure observed with repeated clinic visits (10, 11). However, the response rarely disappears completely and, in some cases, remains large.

It has long been believed that blood pressure initially goes through a labile phase before becoming established at a high level. This is not true. The opposite occurs. Lability increases as the blood pressure level rises, though less than when expressed as a percentage of the mean pressure; it also increases with increasing age (9, 12). Clinical physiologists have shown that blood pressure becomes more variable as the sensitivity of the baroreflexes declines in hypertensive subjects (4, 5) and, strangely, the variations in heart rate decline as the blood pressure variability increases (7, 13). However, when it is realized that the baroreflex influences the blood pressure in large measure by moderating cardiac function, it can be appreciated that, as the baroreflex sensitivity declines, the heart rate will increase and its variability will decrease.

Variability in blood pressure has limited clinical importance. The severity of blood pressure, as revealed by left ventricular hypertrophy and fundus changes, has been reported to be more closely related to the average level of ambulatory blood pressure recorded at home than to pressures measured in the clinic. Variability does not seem to be predictive (14). Though more data are needed, the morbidity and mortality rates due to hypertension have been reported to be better correlated with the average ambulatory blood pressure level than with the clinic blood pressure measurement (15). Left ventricular hypertrophy is also more closely related to raised home blood pressure levels than to the clinic readings (13, 16, 17). The present evidence, though not conclusive, suggests that readings taken in the home environment may be of greater value in clinical assessment than the office readings; the latter are often higher, the rise in blood pressure occurring when a patient visits the physician. The readings obtained at home also appear to be a reasonable guide to prognosis.
Clinical value of self-measurement

Self-measurement for the assessment of blood pressure is of clinical value in several ways.

*Confirming the diagnosis of hypertension* Repeated measurement of blood pressure in the clinic shows that approximately 50% of patients with mildly elevated pressures ultimately become normotensive (10, 11). This can be achieved almost immediately by self-assessment at home and unnecessary treatment can be avoided. Following the established criteria, the upper limit of normal blood pressure for home readings may be taken as 140/90 mmHg or 18.7/12.0 kPa (this applies to casual measurements also). Of course, a blood pressure exceeding 140/90 mmHg does not necessarily indicate that drug treatment is advised, but some intervention in life-style would certainly have to be recommended (18).

*Assessing the effects of therapy* Measurements in the clinic may not accurately monitor blood pressure responses to therapy (19–21). The reliability and accuracy of home readings have three advantages: (1) The target pressure can be defined clearly; the aim should be a diastolic pressure of < 90 mmHg. (2) An excessive reduction in pressure, which may occur if one follows the clinic readings, can be avoided. (3) The interval between clinic visits can be made longer.

Self-measurement of blood pressure provides the possibility of an individually tailored drug treatment. It is complementary to drug studies; any placebo effect in self-measurement will become attenuated or even eliminated in the course of time, so that the blood-pressure-lowering effect of different kinds of treatment can be measured more easily and more reliably.

Further advantages

The availability of self-measurement may lead to the detection of an elevated blood pressure in persons previously unaware of the problem.

For individuals with borderline hypertension, the data collected may be helpful in documenting blood pressure patterns, which may assist in determining the proper treatment regimen. Self-measurement at home may encourage the patients and members of their family to participate more actively in the treatment programme. In some patients, the self-obtained evidence of a fall in blood pressure may encourage adherence to the prescribed treatment (i.e., improved compliance). The home readings may also aid the physician in modifying the treatment and in evaluating the effects of therapy; this could lead to simplification of treatment, including a reduction of drug dosage and fewer side-effects.

Concerns about self-measurement

On balance, the concerns about self-measurement of blood pressure must be weighed against the benefits. The problems include the possibility of inadequate training in measurement technique, consequent inaccurate readings, and misunderstanding of the observed values.
A single or even several self-measured elevated blood pressure readings are not an adequate basis for assuming that a person has hypertension. Elevated readings obtained in this way are only an indication that further evaluation is needed. The diagnosis of hypertension can only be made by a physician who interprets the significance of self-measured blood pressure readings along with other data relevant to the individual.

Repeated high readings due to a defective machine can lead an individual to a false self-diagnosis of ‘high blood pressure’. Users should be made aware of the possibility and implications of such measurements. Similarly, inaccurate low pressure readings also occur in a small proportion of persons.

Self-measurement may not suit some patients who become too concerned with their readings and alarmed by the normal fluctuations in pressure associated with daily living. Misinterpretation or overreaction to one or more measurements may cause psychological distress and even inappropriate self-adjustment of drug therapy. Such adjustment, without proper medical consultation, may lead to treatment errors or side-effects, or other problems.

It is indispensable that patients should be carefully instructed in the proper use of a blood-pressure-measuring device and on the meaning of the results (see below). The apparatus has always to be used correctly and with care. In addition, the user should be highly motivated, but this is not always the case.

If the cuff is too large or too small for the subject’s arm, false readings may result. When the arm circumference exceeds 36 cm, the usual cuff may give falsely high values. Recommendations on the proper cuff size for a given arm girth are available (22), but have not been universally accepted. A hectic or noisy environment during measurement may also result in an excessively high reading.

THE INSTRUMENTS

Two classes of instruments used for the self-measurement of blood pressure will be discussed: portable devices for home measurement and stationary machines, usually installed in public places. A third class of instruments, ambulatory 24-hour blood-pressure monitors, require a high degree of the patient’s cooperation and will not be discussed in this paper. These instruments are used mainly for investigative, sometimes diagnostic, purposes by specialist physicians and are not for self-measurement in the home.

Home blood-pressure-measuring devices

Several million families have already purchased a home blood-pressure measuring device. These instruments may be a mercury sphygmomanometer, an aneroid manometer, or an electronic device.

The mercury sphygmomanometer is calibrated when manufactured and recalibration is unnecessary as long as the meniscus of the mercury column is exactly at 0, when the cuff is deflated. If the mercury column is not at 0 or if it is dirty, the instrument should be returned to the manufacturer for cleaning and recalibration. The
mercury sphygmomanometer is considered the most accurate and reliable device when properly used, and is the standard against which all other blood pressure instruments are compared.

Most instruments for self-measurement include a blood pressure cuff, an aneroid manometer and a stethoscope. These are expected to be reliable, accurate, and relatively inexpensive; to ensure consistent accuracy they should be calibrated at least once a year against a standard mercury sphygmomanometer using a Y-connector (23, 24).

The new digital readout (electronic) devices, which are the easiest of the three to use and usually do not require the use of a stethoscope, are more complex instruments. Many of them are fully automated; the push of a button inflates and deflates the cuff. While more expensive, these automated devices may be advantageous for those concerned about their ability to measure pressure accurately. However, because of their greater complexity and sensitivity, they are more likely to become inaccurate and should be recalibrated more frequently than once a year.

Caution: These instruments are highly sensitive. If the cuff with the sensor is improperly placed or if the arm moves during measurement, errors will occur. Patients should be advised to repeat the reading if unusual blood pressures are noted.

Digital readout (electronic) home blood-pressure-measuring devices are being improved. Both instruments sensing the Korotkov sounds and those based on the oscillometric principle are, in most instances, sufficiently accurate for home use, if patients and the responsible health care professionals are aware of the potential problems.

Stationary machines in public places

The automated stationary machine, whether coin-operated or used free of charge, may be found at work sites, pharmacies, airports, and other public places. Evaluation of the commonly used instruments indicates that the readings can vary considerably between machines. The date of the last calibration of the instrument is the only measure of reliability and often this information is not provided for users. When compared with blood pressures taken by trained observers or by the random zero sphygmomanometer, machine-recorded blood pressure readings may vary by at least 5 to 10 mmHg (both systolic and diastolic). The majority of errors are on the high side.

Blood pressure machines in public places should remind the public of the general significance of high blood pressure. On the other hand, there is much doubt about the validity of blood pressure values obtained in this way. As people are usually left on their own to use these machines, the instructions must be unequivocal and easy to execute. Regular calibrations should be carried out and the date clearly indicated on the machine.

People making use of these machines are often under stress owing to noise or physical exertion. Consequently, the values may be higher than clinic or home readings. This enhances the diagnostic sensitivity, but reduces its specificity. Over-treatment may hardly be detected by this procedure. In any case, the machine's
print-out should sum up the conclusions to be drawn from the blood pressure values measured and provide the user with some sensible recommendations.

Users should be informed about the limited reliability of automated or semi-automated stationary machines and urged to seek medical advice before taking any action as a result of a blood pressure reading from one of them.

TEACHING OF SELF-MEASUREMENT

Who should teach?

Teaching of self-measurement of blood pressure should be regarded as a medical intervention which requires competence and takes time. It also requires a good relationship between the patient and the teacher; a good knowledge of the patient's personality is essential. Either a doctor or a qualified nurse can be the teacher.

Who should be taught?

Only patients likely to derive benefit from prolonged practice of self-measurement should be selected. The physician should carefully weigh the possible hazards of self-measurement for the patient, as he would do before any therapeutic intervention. Persons too concerned with their blood pressure levels, or disease in general, should be advised against self-measurement of blood pressure, even against their own wishes. In general, neurotic or anxious individuals are considered unsuitable. Nevertheless, some patients may cope better with their anxiety when given the opportunity of reassuring themselves by self-readings.

Patients or family members, whatever their social or intellectual background, may be selected, provided that they are sufficiently motivated, have the necessary sensory acuity, understand the objective, and are capable of learning the necessary skills. Elderly patients may find the learning of new skills more difficult than younger ones. Patients with physical handicaps, e.g., Parkinson's disease or syndrome, are obviously unsuitable for self-measurement.

What to teach and how?

The objectives the patient should achieve after being taught are:

(i) the correct and systematic taking of blood pressure readings;
(ii) periodic reporting to the treating physician.

The elementary notions to be understood by the patient include the following:

(i) systolic and diastolic values;
(ii) heart (or pulse) rate;
(iii) variability of blood pressure and heart rate (no alarm if occasional values are high or low);
(iv) dependence of measured values on correct placement of the pick-up;
(v) functioning of the instrument;
(vi) self-measurement should not lead to self-medication.

The skills the patient should learn are as follows:

(i) taking at least five minutes rest before measurement;
(ii) placing the cuff in the proper position, with special attention to the position of the pick-up;
(iii) assuming a relaxed body posture and placing the arm and the instrument correctly;
(iv) inflating and deflating the cuff at the proper rates;
(v) in the auscultatory method, using the stethoscope and listening to the arterial sounds and identifying them;
(vi) coordinating the handling of the valve, listening to the sounds, and reading of the manometer figures;
(vii) reading the figures correctly;
(viii) counting the pulse rate (unless indicated by the instrument);
(ix) recording the values carefully and systematically;
(x) checking the instrument for visible shortcomings (e.g., dirty glass tube, faulty valve, leaking rubber tubes or joints).

Repeated teaching sessions are advisable. The patient should also be given written instructions, preferably an illustrated guide. With the auscultatory method, several simultaneous checks of the patient’s reading are necessary using a Y-connector. The patient’s ability to take the pressure correctly should be tested initially, and retested periodically, preferably at 6-month intervals.

SUPPORT FOR THE PATIENT

Self-measurement of blood pressure must be regarded as part of an integrated regimen. Besides the written instructions on how to use the machine and how to evaluate the readings, the patients should be given the possibility of contacting the physician or the nurse, if they feel insecure or alarmed. In case of breakdown of the instrument, especially the automated, electronic devices, the patient should have access to prompt servicing. When advising the patient which instrument to purchase, preference should be given to products for which servicing is readily available. Similarly, the patient should be assisted and, at least once a year, should be reminded (orally or by mail) to have the instrument checked.

The patient’s self-recorded values should be discussed at regular intervals with the physician or nurse; such attention is valuable psychological support and complements the other measures of treatment and management.

ACKNOWLEDGEMENTS

This article includes extracts taken from Hunt JC, Frohlich ED, Moser M,
Roccella EJ and Keighley EA. Devices used for self-measurement of blood pressure. Revised statement of the National High Blood Pressure Education Program. *Archives of Internal Medicine, 145*: 2231 – 2234 (1985). Permission to use the text is gratefully acknowledged. Passages are also quoted from two unpublished documents on self-measurement, prepared by J. Conway and M. Anlauf; their collaboration is much appreciated.

**REFERENCES**


APPENDIX V

The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems

INTRODUCTION

Ambulatory blood pressure measurement is rapidly gaining acceptance as a useful procedure in the clinical management of hypertension (1, 2), in the assessment of antihypertensive drugs (3) and as a means of predicting outcome in hypertension (4). The procedure also provides data on the physiology of blood pressure behaviour (5). Ambulatory blood pressure provides an assessment of blood pressure behaviour over time in the patient’s normal environment and is likely to result in reappraisal of the clinical management of hypertension, which is presently based on conventional measurement techniques (6).

One consequence of the increased interest in ambulatory measurement has been the creation of a large market for ambulatory blood pressure measuring devices. In recent years the number of devices available commercially has risen rapidly, with more than 10 now available on the international market and many others in the planning phase (7). Ambulatory blood pressure measuring systems are expensive,
often costing as much as £4000 ($US6800) for one recorder. Decoding facilities may cost as much again. Operational and maintenance costs may also be considerable. At present there is no obligation on manufacturers to comply with the few recommended standards that are available. There is no standard for automated blood pressure measuring devices in the UK. In the USA, the Association for the Advancement of Medical Instrumentation (AAMI) has produced a detailed standard for semi-automated and automated devices (8).

The present situation, therefore, is that manufacturers may market expensive blood pressure measuring devices without being obliged to provide evidence of their accuracy. Many validation studies of ambulatory blood pressure measuring devices have been performed with a variety of protocols and differing criteria for assessment, making comparison of the assessment difficult and comparison of one device with another almost impossible.

Because validation studies are time-consuming to perform, the time-lag between manufacture and publication of an independent evaluation in a reputable journal is often so long that manufacturers may be ready to market a modification of the original device and the outcome of any evaluation is thereby rendered obsolete and of little academic interest.

The British Hypertension Society (BHS) is of the opinion that evaluation of ambulatory blood pressure measuring systems must be standardized for the following reasons. (1) Continued uncontrolled marketing will inevitably result in the manufacture and sale of inaccurate devices; this has clear implications for clinical practice, the most important of which is inappropriate diagnostic and management decisions; and (2) without a standardized approach to evaluation, comparison of results between laboratories is not possible and work may have to be repeated with the consequent waste of scarce resources.

The BHS Working Party on Blood Pressure Measurement, having reviewed the possible approaches to the problem, concluded that while the AAMI standard (8) is the most comprehensive recommendation on validation available, it has a number of deficiencies; it does not cover all aspects of evaluation, e.g. interdevice variability, ambulatory assessment and patient acceptability are not included and there are deficiencies in the statistical methodology; it is obtainable only from the AAMI offices on payment of a fee, and is not, therefore, as accessible as a journal publication; it contains detailed recommendations for manufacturers of ambulatory devices which, though necessary in a standard, are not a requirement of an evaluation protocol. The Working Party decided, therefore, to prepare a protocol that would serve as a standardized procedure for the evaluation of ambulatory blood pressure measuring devices and to make recommendations for the adoption of this standard procedure. Though the Working Party's brief was to prepare a protocol for ambulatory devices the principles of the procedure that follow can be applied to any automated or semi-automated blood pressure measuring device (9).

**GENERAL CONSIDERATIONS**

The basis of this device evaluation is the comparison between blood pressure measured by the device being tested and simultaneous measurements made by an
established technique, the 'gold standard'. The test methods must allow for variation in the design and technology of ambulatory measuring devices.

Two features of the programme described in this paper need elaboration. First, before embarking on what is a complex and labour-intensive protocol, the Working Party placed considerable emphasis both on observer training and on the capability of a number of devices of the model being tested to give consistent measurements. The AAMI standard recommends that two observers should measure blood pressure independently against the test device in the main validation phase (8). The main advantage of using two trained observers is that the conclusion of the validation test is strengthened by having two independent standard measurements against which to judge the test device (9). If the observers have already been shown to be in close agreement, it is only necessary to have one observer take the measurement. However, to minimize bias, it is advisable that separate observers each measure blood pressure in approximately half the subjects. This modification to the AAMI standard has the advantage of substantially reducing the cost of performing the main validation test.

In this protocol observer agreement is strictly assessed before the evaluation; if an observer is inaccurate re-training is easily accomplished at this stage. However, with the AAMI standard, observer agreement is assessed at the end of the validation, and in the event of the observers not being in agreement the entire procedure has to be repeated. It is preferable that observer agreement be assessed before the study begins so that this eventuality is avoided. If the test standard, namely the mercury sphygmomanometer and the observer, cannot be brought to the highest possible level of accuracy before the main validation procedure, further testing is pointless. Likewise, interdevice variability should be assessed before the validation test begins, since substantial differences between devices of the same model will render device validation impracticable.

Second, in drafting this protocol we attempted to determine the minimal criteria for a statistically valid assessment while also being alert to the demands that the validation tests impose on an assessment laboratory. Whereas it might be desirable to perform the main comparative validation when the device is new and repeat the test after a period of time in use, this would effectively nearly double the time and expense of the study. We compromised, therefore, by postponing the main validation test until the device has been in use for a period of time, and we arbitrarily chose a minimum period of 1 month. We believe this to be justified on the basis that the accuracy of a measuring device after use is of more relevance than immediately after purchase, before it has been subjected to the wear and tear stresses of daily use that might alter accuracy.

Unlike the AAMI standard (8), direct intra-arterial measurement is not included in the present protocol for the following reasons. First, systolic and diastolic blood pressure values obtained by the direct technique are different from measurements obtained by indirect methods (10, 11). Second, clinical practice uses data obtained by the indirect rather than the direct technique. Third, there are ethical considerations in the use of intra-arterial measurement which preclude its use for the evaluation of blood pressure measuring devices in most laboratories.

In an effort to minimize unnecessary testing, the programme has been designed so that the device passes through different phases of evaluation, entry to each test
phase being dependent on the successful completion of the preceding phase.

A standard mercury sphygmomanometer, the components of which were carefully checked before the study, is used as a reference standard for all tests rather than a random zero sphygmomanometer (12) because there is evidence that the random zero sphygmomanometer systematically underestimates diastolic pressure (13–16).

The quality of the stethoscope is also crucial to the evaluation procedure. Stethoscopes with badly fitting earpieces and poor quality diaphragms preclude precise auscultation of Korotkoff sounds. The Littman stethoscope (3M Company Minnesota, USA) or its equivalent is recommended.

The general principles of auscultatory measurement have been outlined in previous publications of the British Hypertension Society (17, 18).

In the protocol we use the term model to denote a particular brand of sphygmomanometer and the term device to denote individual sphygmomanometers.

METHODS

The evaluation programme consists of six phases (Fig. 1): I, Observer training and assessment; II, Before-use interdevice variability assessment; III, In-use assessment; IV, After-use interdevice variability assessment; V, Device validation; and VI, Preparation of report.

Phase I: Observer training and assessment

Observer training

Two trained observers are required for the evaluation of a device. Each training day consists of two phases.

Film training The observers, each of whom should understand the principles of blood pressure measurement, e.g. trained nurses, are retrained in blood pressure measurement using the British Hypertension Society video film Blood Pressure Measurement (19). It is recommended that audiograms are obtained from the observers to detect any hearing deficit. The first part of the film training demonstrates the technique of blood pressure measurement and is followed by an assessment period in which the trainees can test themselves against a standard mercury sphygmomanometer as the mercury column falls against a background of recorded Korotkoff sounds. Observers should not move on to the next stage until they have satisfied this assessment. The video film lasts 30 min.

Expert training In this phase, an expert in blood pressure measurement takes the trainee observers through the different stages of measurement as recommended by the British Hypertension Society (17). Difficult aspects of interpretation, such as the auscultatory gap and bias, should be discussed and illustrated by example using a multi-aural stethoscope.
Observer assessment

Two (or more) observers are tested for accuracy against each other and against an expert observer. The expert observer should have had extensive experience in blood pressure measurement and he/she should have correctly interpreted 95% of a test sequence, e.g. the sequence in the British Hypertension Society video (19), before each training assessment. If the expert observer is inaccurate this will become apparent in the analysis.

The test procedure takes the following form (Fig. 2):

1. Two observers are seated at a bench fitted with temporary partitions so that each observer is isolated in a booth in which the only objects are a mercury
column, a stethoscope, a pencil and a blank sheet of paper. When more than one observer is being trained and assessed it becomes difficult to prevent an observer who is unsure of a reading from gaining sight of a neighbouring observer's reading, and it is necessary, therefore, to separate the observers by a series of partitions.

(2) In a similar adjoining booth an expert observer deflates a bladder attached to the arm of a subject.

(3) The subjects' blood pressures should be in the range 110/60 to 240/120.

(4) The bladder is connected to each of the columns of mercury in the observer booths so that all columns of mercury fall simultaneously for each of the blinded observers and the expert, all of whom write down their measurements.

(5) Ten measurements are made by each observer on each of five subjects giving a total of 50 measurements for each observer.

The accuracy criteria for the test procedure are:

(1) 90% of systolic and diastolic differences between trainees and the expert may not differ by more than 5 mmHg and 98% by not more than 10 mmHg;

(2) 85% of systolic and diastolic differences between each trainee may not differ by more than 5 mmHg and 95% by not more than 10 mmHg;

(3) failure to achieve this degree of accuracy requires a repeat training and assessment session for the failed observer(s).

Familiarization session

As devices for ambulatory blood pressure measurement are complex, familiarization is important. The observers should be instructed in the use of the devices to be
tested, preferably by a representative of the manufacturer. Practice measurements should be made on a number of subjects.

**Phase II: Before-use interdevice variability assessment**

If only one device is tested for validation, it is possible, in the event of the assessment proving unfavourable to the test device, that the device is unrepresentative of the product and the inaccuracy might have been due to poor calibration or to some other fault that might occur only occasionally (20). It is also possible that the first device to be tested might be accurate but unrepresentative. Because of these potential differences between machines we suggest that at least three devices should be tested for interdevice variability before proceeding to validation, and if differences emerge between devices further testing should not be conducted until the manufacturer has identified the source of error and provided three devices which are in agreement. The recommendation to select three devices is based on economic and feasibility considerations.

Semi-automated devices for blood pressure measurement should have a facility permitting connection with a mercury sphygmomanometer to check device calibration, and it is likely that future models of devices which presently do not readily lend themselves to calibration will provide this facility. Although calibration details vary from one system to another, the test is usually performed by connecting the device to a mercury sphygmomanometer with a Y-connector. The automatic pressure measuring system and the blood pressure detection mechanism (i.e. microphone, oscillography, etc.) are disabled so that the device acts simply as a manometer. Pressures within the system are then compared throughout the pressure range on the mercury column.

**Test requirements**

The test requirements are:

1. 95% of measurements should be within 3 mmHg or 2%, whichever is the greater.
2. If the device fails to meet the manufacturer's calibration criteria it is not tested further.

**Phase III: In-use (field) assessment**

The three devices used for the interdevice assessment are next used to test the accuracy and performance of the device during and after the use for which it was designed, i.e. 24-h ambulatory monitoring. The purpose of this phase is to subject the ambulatory blood pressure measuring system to a period of fairly strenuous use before performing the main validation test. Each of the three devices are placed on six subjects with a wide range of pressure on 8 days over a 4-week period. At the end of this period the performance of the device is assessed.
Test requirements

The test requirements are:

(1) Each of the three devices it to be worn for 24 h by eight subjects with a wide range of pressures using a total of 24 subjects.
(2) 24 h ambulatory measurements are taken at 15 min intervals from 0900 – 2200 h (56 measurements), and at 30 min intervals from 2230 – 0830 h (19 measurements), giving a total of 75 readings for the 24 h;
(3) 600 recording per device are taken;
(4) 1800 recordings per model are taken.

TABLE 1. Example of in-use assessment

<table>
<thead>
<tr>
<th>Subject</th>
<th>I</th>
<th>V</th>
<th>V/1%</th>
<th>R</th>
<th>A</th>
<th>V (D)</th>
<th>V (N)</th>
<th>D:N ratio</th>
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</tr>
</tbody>
</table>

Total 2104 1734 83 14 339 1405 346 4.1:1
Ideal 1800 1800 100 0 0 1440 360 3:1

I = Number of inflations; V = number of valid readings; V/1% = Percentage of valid readings per inflation; R = rejected; A = aborted; D = day; N = night.
Performance criteria

The performance criteria are:

(1) Most ambulatory blood pressure measuring systems have programmed editing criteria and these are left in operation for this phase. If the instructions allow the operator to modify the editing programme, the programme recommended by the manufacturer is chosen.

(2) The measurements obtained over each 24 h period are classified as follows (Table 1):
   (a) Inflations. The total number of inflations made by the device.
   (b) Valid readings. Those readings accepted by the system as genuine blood pressure measurements.
   (c) Rejected readings. Those blood pressure readings that are rejected either by the recorder or the decoder as not being genuine blood pressure measurements.
   (d) Aborted readings. Those occasions when an inflation fails to produce a reading of any kind.
   (e) Day/night readings. The ratio of valid day/night readings.

(3) If a device fails to record any pressure in the 24 h period and/or the subject may not have complied with instructions on a particular recording day, that 24 h recording is repeated.

(4) At least 70\% of readings should be valid for 22 of the 24 recording days.

(5) Failure to achieve this level of performance means that no further testing is carried out.

The purpose of this phase is to ensure that a period of time in use does not make the system inaccurate; it is not intended primarily as an assessment phase though the information on performance may be useful. However, there is little point in proceeding to the main validation test if the device performs extremely badly as an ambulatory recording system.

Patient/subject acceptability

In this assessment each subject is asked to make comments on the following aspects of device performance which are printed as headings, allowing five or six lines for comment on each topic. While this is not an elimination stage, the information may be helpful later in making an overall assessment of performance, and the comments may indicate areas of improvement for the manufacturer. The headings for comment are:

List any problems
General impression
Comfort/discomfort
Interference with activity
Interference with sleep
Problems with noise
Anxiety factors
Difficulty in using
Clarity of user instructions
Comparisons with other devices used by subject
Suggestions for improving device

The subjects should be asked to keep a diary card in which they are asked to make a particular note of activity at the time of each ambulatory measurement.

Phase IV: After-use interdevice variability assessment

At the end of the month of ambulatory assessment the three devices are retested for interdevice variability, as in the before-use interdevice variability test, to determine whether there has been any change in interdevice agreement after use.

If all three devices give measurements that are in agreement at the time of purchase as well as after a period in use, it suggests, at least, that the model is being manufactured to perform consistently. If, however, all three devices give discordant measurements, further assessment is pointless and the model cannot be recommended. If one device is discordant but the remaining two are consistent, further evaluation is reasonable on the basis that one inaccurate device might have been included by chance. This occurrence may indicate, however, that overall production of that model is not satisfactory and the finding should be included in the final report. If only one device is discordant it is removed while the other two are retained for the validation test. If all three devices are discordant no further testing is carried out.

Phase V: Device validation

If there has been no alteration in interdevice variability after the month of use, one device is arbitrarily selected from the three devices for the main validation test. Because blood pressure measuring devices are of varying designs it is necessary to allow some flexibility in the validation methodology. The following tests allow validation of devices with controllable and rapid deflation rates.

Subject selection

In the selection of subjects it is not sufficient to merely specify that subjects shall have blood pressures within a specified range [as required by the AAMI standard (8)] because there may be a tendency (arising out of convenience) to recruit more subjects in the lower pressure range than those with higher pressures.

The tests should be performed with the adult bladder supplied with the device; the dimensions should be noted and a similar bladder should be used for the comparative test. The circumference of the arms should be measured to ensure that the bladder being used is adequate for the subject, i.e. the bladder should be of sufficient length to encircle 80% of the arm circumference; only the cuff and bladder should be changed for obese arms, since it is important to ensure that the same microphone is used throughout the validation test.

Subject selection is also dependent on the circumstances under which the device will be used. If the device is intended for a special patient population, such as preg-
nant or paediatric patients, it must be validated in these groups; the recommendations in this paper are for adult patients. Likewise, patients with arrhythmias, such as atrial fibrillation, should not be included; if validation in these circumstances is required subject selection must be directed accordingly. Subjects in whom Korotkoff sounds persist to near zero should be excluded from the study.

The criteria for selection are as follows:

(1) 85 subjects;
(2) age range 15—80 years;
(3) at least 15% of blood pressures in each of the following categories of systolic pressure (mmHg): 100—140, 140—180, 180—220, 220—240;
(4) at least 20% of blood pressures in each of the following categories of diastolic pressure (mmHg): 60—80, 80—100, 100—120.

*Devices with controllable deflation rates*

This test is based on simultaneous same-arm measurement between the test device and a standard mercury sphygmomanometer. It is the ideal test, and blood pressure measuring devices should incorporate the facility for this form of validation. The test should be performed in a warm, quiet room. The procedure is as follows:

(1) Connect the test device via a T-tube to a standard mercury manometer and pump bulb (Fig. 3).
(2) Place the cuff of the test device on the subject’s arm according to the manufacturer’s instructions.
(3) For auscultatory devices, place the microphone over the brachial artery.
(4) For devices with ECG gating, place the electrodes according to instructions.
(5) The inflation mechanism of the device is activated and one observer records pressure simultaneously with a stethoscope and mercury sphygmomanometer in 43 subjects and a second trained observer does likewise in the remaining 42 subjects (the subjects should be distributed between the observers to ensure that each

![Diagram](image)

*Fig. 3. Design for simultaneous measurement between mercury standard and test devices.*
observer has a representative number of subjects with high and low pressures).

(6) An independent observer charts the pressure reading of the device so that neither observer is aware of the other’s reading.

(7) Three measurements are made by each observer and tabulated for analysis of systolic and diastolic values; these measurements are not averaged as recommended in the AAMI standard because by so doing, the variability of error within a particular subject may be eliminated, thus incorrectly indicating greater accuracy.

(8) A total of 255 measurements between observers and the test device are analysed.

(9) Documentation must be provided for data omitted for legitimate technical reasons; once a subject is included, before the data-gathering phase, the data for that subject should not be excluded from the study if blood pressure values are obtainable; if blood pressure measurements from either the reference method or the ambulatory device are unavailable, data entry for that subject may be excluded with an accompanying explanation, and additional subjects must then be entered into the study to ensure a sample size of 85.

**Accuracy criteria**  The percentage of test device measurements differing from the mercury standard by 5, 10 and 15 mmHg or less are calculated (Table 2) and plotted (Appendix A; Figs 4 and 5); the device is then graded as A, B, C or D according to the criteria in Table 3. To reach a particular grade all three cumulative percentages should exceed the tabulated values. Though the mean, standard deviation of measurements and the mean and standard deviation of the differences are not used for grading purposes, they should be provided, as in Table 2, for information.

**Devices with rapid deflation rates**

The above test cannot be performed with devices that deflate at rates greater than 5 mmHg/s because faster rates do not allow a sufficiently accurate measurement by

<p>| TABLE 2. Example of device validation for two paired measurements of systolic and diastolic pressures in 85 subjects |
|-------------------------------------------------|-----------------|-----------------|------------------------------|-----------------|</p>
<table>
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<tr>
<th>Obs./device</th>
<th>n</th>
<th>Mean ± SD</th>
<th>Difference ± SD</th>
<th>Readings (%)</th>
<th>Grade</th>
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<td></td>
</tr>
<tr>
<td>Obs. 1</td>
<td>127</td>
<td>91 ± 15</td>
<td>-2 ± 6</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>Device</td>
<td>127</td>
<td>88 ± 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs. 2</td>
<td>128</td>
<td>151 ± 22</td>
<td>-2 ± 6</td>
<td>66</td>
<td>87</td>
</tr>
<tr>
<td>Device</td>
<td>128</td>
<td>148 ± 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs. 2</td>
<td>128</td>
<td>90 ± 12</td>
<td>-1 ± 5</td>
<td>74</td>
<td>92</td>
</tr>
<tr>
<td>Device</td>
<td>128</td>
<td>89 ± 12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Observers (Obs.) 1 and 2 measured blood pressure in 42 and 43 subjects, respectively.
### TABLE 3. Grading criteria based on cumulative percentage of readings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Difference between standard and test device (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 5</td>
</tr>
<tr>
<td>A</td>
<td>80</td>
</tr>
<tr>
<td>B</td>
<td>65</td>
</tr>
<tr>
<td>C</td>
<td>45</td>
</tr>
<tr>
<td>D</td>
<td>Worse than C</td>
</tr>
</tbody>
</table>

*Fig. 4.* Plot of pressure difference and mean pressure for test device and observers in 85 subjects for systolic pressure (*n* = 255). Reference lines for 0, ± 5, ± 10 and ± 15 mmHg differences are shown.

An auscultating observer, leading to an inaccurate comparison between the test and the reference device (21). At fast deflation rates an auscultating observer will tend to underestimate systolic and overestimate diastolic pressure by recording the first definite pressure phase at which Korotkoff sounds are audible as the systolic value and the last definite phase of audible sounds as the diastolic. The device may have
a facility for slowing the rate of deflation so that the above test can be performed but it is important to determine that this modification of the usual operational mode does not alter the accuracy of measurement. Other factors that may preclude simultaneous same-arm testing are confusion between noise from the device and the Korotkoff sounds, failure of the inflating mechanism to reach the required pressure, and uneven deflation, making accurate auscultation impossible.

The alternatives to simultaneous measurements in the same arm are either simultaneous measurements in the opposite arms or sequential measurements in the same arm. We favour the latter approach because if simultaneous measurements are to be performed in opposite arms it is necessary first to determine that the interarm differences are small enough to prevent the introduction of error; this would require simultaneous measurements in both arms in all 85 subjects, a major undertaking in itself. Furthermore, sequential same-arm measurements are closer to simultaneous same-arm measurements than opposite arm measurements (Appendix A).

Sequential same-arm measurements between the test device and a standard mercury sphygmomanometer are carried out as follows:
(1) A trained observer measures blood pressure with a stethoscope and a mercury sphygmomanometer deflating at 2 mmHg/s.
(2) One minute later, measurement is made in the same arm with the test device, which is 'blinded' from the observer.
(3) One minute later again, the observer repeats a measurement with the mercury sphygmomanometer.
(4) The sequence 2–3 is repeated three times in 85 subjects to give 255 readings.
(5) The difference is calculated. If the device pressure lies between the first and third pressure the difference is zero; otherwise, the nearer of the two readings is subtracted to give the difference.
(6) The data are recorded and analysed as for devices with controllable deflation rates.

Phase VI: Report of evaluation

The final report should be prefaced with subject data that define the key characteristics of the subjects in the study; these data should include the number of subjects, the ranges of systolic and diastolic pressures and the numbers of subjects for each pressure level, age and arm circumference measurement.

Assessment of basic user information and service/maintenance facilities

All technical problems encountered during the validation tests are recorded, so that the information is available for reference, including a description of any problems encountered, the date of occurrence of any breakdown, date of repair, effect on validation procedure, comments on agency/manufacturer efficiency, estimated costs of service and appropriate recommendations to the manufacturer for improving the equipment.

Basic information

The information provided in operational manuals is often deficient. Without appropriate specifications and operational instructions it is difficult to obtain an optimal performance. The information listed in Appendix B should be provided and deficiencies in this regard should be listed in the report.

Acknowledgements

The report should state whether the equipment was purchased for the evaluation or if it was donated by the manufacturer. The data analyses should be carried out by the laboratory doing the evaluation. If the analyses were carried out by the manufacturers, this should be stated.

DISCUSSION

The expanding role of ambulatory measurement is creating a large potential market
and it is important to anticipate the consequences of uncontrolled proliferation of very expensive ambulatory systems which are not subjected to critical evaluation. The Working Party on Blood Pressure Measurement of the British Hypertension Society, which has previously made recommendations on the accurate measurement of blood pressure (17, 18, 22) was given a mandate by the Society to prepare recommendations for the evaluation of ambulatory devices. When the Working Party began considering the problem it appeared that the AAMI standard (8) might be adopted with minor modifications as a standardized protocol for the general evaluation of ambulatory devices. However, careful consideration of the AAMI standard revealed a number of methodological and statistical problems and it was considered necessary to draft a protocol directed specifically at evaluation of ambulatory devices for clinical use, rather than dealing (as the AAMI has done very effectively) with manufacturing standards. In so doing, the Working Party acknowledges gratefully the strong influence that the AAMI has had in initiating thinking in this complex subject, and many of the AAMI recommendations are incorporated in this protocol.

One drawback of the AAMI standard is that it is not published in a medical journal. Of greater importance is the failure of the standard to provide a test for interdevice variability, a test for the device in the ambulatory setting and a test for accuracy after a period of use. This protocol addresses these areas as well as making recommendations on the information that should be supplied by the manufacturer, and permits an assessment of patient acceptability of the device. Though this protocol provides an assessment of performance during ambulatory use it is important to recognize that blood pressure measurements are usually made with the subject at rest; an ambulatory device that meets the criteria of the present protocol cannot be assumed to be accurate during physiological manoeuvres, such as exercise, isometric handgrip, Valsalva manoeuvre, etc. Moreover, the protocol does not test the device in the variety of positions in which ambulatory measurement may be made.

Since the AAMI standard was published, methods of statistical analyses in the evaluation of devices have also changed. Most notably, the correlation coefficient, once regarded as the basis of comparison for studies of one device against another, has been largely abandoned because it may suggest close accuracy when there are, in fact, gross differences between the devices being compared (23, 24). Therefore, more suitable statistical methods are recommended here.

We regard the AAMI criteria of acceptable inaccuracy (mean difference of ± 5mmHg with a standard deviation of 8 mmHg) (8) as too liberal. We have devised, therefore, a system of grading, grade A being an unachieved accuracy level to date, which it is hoped future ambulatory devices will attain.

The Working Party is conscious that following the recommendations in this protocol is an onerous task and has endeavoured to keep the procedures as simple as possible. Towards this end, the entire procedure has been designed to ensure that expensive and time-consuming tests are not performed on devices which do not meet certain basic accuracy criteria. For example, the most difficult test, the main validation test requiring the participation of 85 subjects with a wide range of pressures, is not performed until the device has been field tested and proven not to have developed interdevice variability during a period of ambulatory use. The procedure, nonetheless, is necessarily lengthy and requires considerable involvement of trained
personnel and careful supervision, but if ambulatory measurement is to realise its full potential it is imperative that strict standards are applied without delay.

However, the adoption of these standards by the manufacturers of blood pressure measuring devices may not be easily effected. Manufacturers cannot be obliged to guarantee the accuracy of their product, though it is likely that the legislative harmonization being prepared by the Commission of the European Communities with regard to essential safety requirements of medical devices will be extended to other aspects of device performance, such as accuracy (25). Also, we expect that reputable manufacturers will welcome the opportunity of having ambulatory blood pressure measuring devices evaluated independently according to a generally accepted protocol. Unfortunately, the presence of a national standard is not a guarantee of accuracy and it will be many years before there is any acceptable standard in Britain and Ireland. The British Standards Institution is presently preparing a standard for automated devices. The British Hypertension Society has made application to the Institution for a standard for semi-automated devices (personal communication to E.O’B.). However, even if there was an acceptable standard for ambulatory devices, manufacturers would not be obliged to comply with it and the need for independent evaluation would still exist.

Manufacturers of ambulatory blood pressure measuring systems must be encouraged to have their product evaluated independently according to an approved evaluation procedure. This process, which will necessarily take time, could be influenced beneficially if editors of general medical, clinical pharmacology and hypertension journals critically evaluated the evidence supporting the accuracy of ambulatory blood pressure measuring systems used in research studies. Health authorities and sponsoring organisations should not continue to purchase equipment which has not been evaluated adequately.

REFERENCES

ometers for home measurement of blood pressure. *J Hypertens* 1990; 8: 621–635.


**APPENDIX A: STATISTICAL CONSIDERATIONS**

**Introduction**

Different observers and different devices never agree exactly, in the sense of giving the same blood pressure for all subjects. The comparison of two sets of blood pressure readings thus takes the form of assessing the amount of disagreement. Methods of comparison are described and illustrated in this appendix. However, statistical methods cannot indicate what is or is not acceptable agreement for an individual subject or a group of subjects; this decision must be based on clinical considerations.

Whether two observers or two devices are compared, the philosophy of the recommended approach is to consider the distribution of the differences between the blood pressure obtained for each individual
subject. If more than two sets of measurements are available the same approach is used to compare each pair. Graphs are particularly useful. There is no place in this analysis for the calculation of correlation coefficients or hypothesis tests.

Initial analysis

In the presentation of evaluation data it is common practice to begin by producing a scatter plot of the two sets of blood pressure data (observer and test device). These plots usually show systolic and diastolic pressures separately, although they can both be shown in a single plot. The scatter plot can be a useful first step, but it is inefficient as all the information is usually clustered near the line. We have, therefore, used a better way of assessing the discrepancies by plotting the differences between the measurements of the observer and the device, against their average, as in Figures 4 and 5. This plot shows the differences in blood pressure explicitly, and also indicates whether the distribution of the differences varies according to the level of blood pressure. We use the average blood pressure here, as this is the best estimate of the true blood pressure for that patient at that time. This method of plotting, which can be extended to give more information (see below), is recommended in preference to the conventional scatter plot.

Quantification of agreement

The assessment of agreement is based on both the average differences between the methods of measurement and the variability in the differences. The average agreement between the two sets of blood pressure measurements is the mean of the differences from each subject (and is equal to the difference between the overall means). There are three approaches to the assessment of the variability component of agreement:

1. The proportion of differences that are greater than some reference value, say 10 mmHg, can be calculated. The reference values can be superimposed on the scatter diagram.

2. The values outside which a certain proportion, say 10%, of the observations fell can be calculated. This is done simply by ordering the data and taking the range of values left after a percentage of the sample is removed from each end. These values can also be superimposed on the scatter diagram.

3. The standard deviation of the intrasubject differences can be calculated. On the assumption that the differences will be normally distributed, which is usually reasonable for blood pressure data, the range of values expected to encompass most intrasubject differences can be calculated. For example, 90% of differences can be expected to lie between the mean $-1.645 \times SD$ and the mean $+1.645 \times SD$. These two values are called the 90% limits of agreement. They can also be superimposed on the scatter diagram.

Methods (1) and (2) do not require any assumptions about the distribution of the differences, but they are generally less reliable than those obtained using normal distribution theory, especially in small samples. However, if there are one or more outliers (extreme discrepancies between observers or methods), an empirical approach may be preferable. In this protocol, we have chosen to use the percentage of differences within certain limits (Method 1), a simple approach that can be used for all phases of the evaluation. For the device validation phase (Phase V) three of these assessments are made, relating to the percentage of differences within 5, 10 and 15 mmHg. A device is then graded according to these results using the criteria in Table 3.

Grading and method of validation

Table 4 illustrates the rationale for calculating the differences in the sequential test, using the grading criteria given in Table 3. In this analysis, 85 subjects with a wide range of blood pressure had simultaneous measurements taken with mercury sphygmomanometers by two trained observers in the same arm and simultaneously in the opposite arm by a third trained observer, the sequence being
TABLE 4. Effect of test methodology on grading analysis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differences between standard and test device (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 5</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>89</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>91</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>74</td>
</tr>
<tr>
<td>B</td>
<td>64</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>69</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>84</td>
</tr>
<tr>
<td>B</td>
<td>85</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>92</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; SBP = systolic blood pressure.

repeated three times so as to provide sequential measurements in both arms. The results in the table, therefore, are derived from 255 measurements.

In the first two lines, the grades for simultaneous same-arm measurements are shown and Grade A status is reached for both systolic and diastolic pressures. This is the 'gold standard'. In the second pair of lines, the data for simultaneous opposite-arm measurements are presented and a Grade B rating is obtained for systolic and Grade C for diastolic pressure; clearly this analysis is much inferior to the first.

In the third pair of lines (sequential I) same-arm sequential measurements are analysed, the differences being calculated by comparing the mean of the first and third mercury measurements with the second measurement (which corresponds to a test device); a Grade A rating is achieved for systolic but only a Grade B for systolic pressure. Clearly this is better than opposite-arm measurements but is not as good for systolic pressure as simultaneous same-arm measurements. However, this analysis is mathematically flawed in that the relationship between the first and third mercury measurement is assumed to be linear, which need not be so. In the fourth pair of lines (sequential II) the analysis is based on the assumption that the difference between the first and third blood pressure reading need not be linear, and the difference is calculated as follows. If the second (test) pressure lies between the first and third pressure the difference is zero; otherwise the nearer of the two readings is subtracted to give the difference. This correction technique restores the sequential analysis to parity with the simultaneous same-arm analysis by bringing the systolic rating to Grade A.

Power

The calculation of an appropriate sample size for the device validation (Phase V) is, to some extent, arbitrary. If the observed proportion of differences within 5 mmHg is 80%, then a 95% confidence interval for this proportion will be ± 5% with a sample size of 85 subjects (225 observations), the size recommended in the AAMI standard (8). We believe that a smaller sample may be acceptable, but we have decided to remain with the AAMI recommendations of 85 subjects until working data become available as the protocol is used, when it may be possible to make power calculations that would effect a reduction in this large sample size.

APPENDIX B: BASIC INFORMATION

*Model identification* When manufacturers incorporate modifications into externally identical or in-
distinguishable versions of a model, this should be clearly indicated by model number and full details as to how the model differs from earlier versions should be provided. In particular, the likely effect of all such modifications on the performance and accuracy of the model should be stated.

Costs The cost of the recorder, the decoder, computer analysis facilities and all components should be listed. The consumables needed for device operation and their cost should be provided.

Compliance with standard(s) The standard adopted by the manufacturer should be stated.

Validation studies and results The results of validation assessments by the manufacturer and/or by independent laboratories should be summarized to provide the following details: the method of validation, the number of subjects, any special features in subject selection, e.g. pregnancy, childhood, the range of blood pressures, the heart rate range, the accuracy requirements and the statistical analysis employed. The full references for all published validation studies should be listed together with the addresses of the laboratories.

Instructions for use These should be clearly stated in a step-by-step layout. Illustrations are helpful in this context.

Patient instruction card A card should be provided for distribution to patients using the ambulatory recorder, which gives simple operational instructions together with instructions as to what precautions to take in the event of the device malfunctioning.

Power supply The mains voltage and the frequency must be shown and whether or not a transformer is needed to adapt the decoder. If the latter applies, the frequency must also be converted as the movement of certain parts may be affected, with resultant inaccuracies. The most suitable batteries for the device should be listed and those capable of being recharged should be indicated. The number of recordings obtainable for a set of batteries, or per charge, and the warning system for battery failure should be indicated.

Instructions for care and maintenance The operator should be given clear instructions on the day-to-day care of the equipment and the need for regular maintenance. Product warranty information should be provided. Ambulatory devices should have full warranty cover for at least 1 year after the date of purchase.

Service facilities The location of national and international service facilities should be listed. It is regrettable that some manufacturers appoint agents who, though competent with certain ranges of medical devices, have little or no knowledge of specialized blood pressure measuring equipment. Potential purchasers should be aware of this problem and check that the agent is competent to provide the necessary facilities. An estimate of the cost of routine servicing out of warranty together with an estimate of the costs of transporting the equipment for servicing should be given. Maintenance contracts are available for some ambulatory systems and details of these should be provided.

Dimensions The dimensions of the recorder and its total weight with batteries, pump, etc., should be indicated. The means of attachment, waist-belt, shoulder-strap, or bag, etc., should also be stated.

List of components All major components of the system should be listed. The dimensions of the bladders supplied and the dimensions of the range of bladders available should be indicated. A 35 × 13 cm bladder is strongly recommended for routine use in most adults by the British Hypertension Society (17).

Method(s) of blood pressure measurement The basic method of pressure detection, e.g., auscultatory
or oesophageal, should be stated and if more than one method is used the indications for changing methods and the means of denoting this on the recording should be stated. With Korotkoff sound detecting devices, the use of either Phase IV or Phase V as the diastolic end-point must be disclosed. If data are derived from recorded measurements, such as mean pressure, the method of calculation must be stated.

**Artefact editing** Some ambulatory devices have inbuilt systems for editing artefactual measurements. The method of doing this and the rationale should be stated. Reliable and accurate devices should require only minimal editing and this should be performed automatically by the device. It should not be necessary for the operator to have to screen the device measurements for bizarre recordings that are likely to be artefactual. We have refrained, therefore, from making recommendations on artefact editing.

**Facility for checking device accuracy** Blood pressure measuring devices should be provided with a facility for accuracy assessment against a reference system whereby simultaneous measurement can be performed on the same arm with the device which is being tested and the reference system. Some ambulatory systems function with rapid deflation rates but in some models it is possible to switch to a slower deflation rate. These devices should be tested using the rapid deflation rate, as switching to a slower mode may give results which do not reflect the accuracy of the device in use. Special consideration has to be given to the method of testing and to the interpretation of data with these devices.

**Facility for device recalibration** The manufacturer should state the intervals at which recalibration becomes necessary and a simple method for checking accuracy should be provided. If recalibration is required, the manufacturer should state whether this can be done by the owner, and if so, how.

**Factors affecting accuracy** Many factors may affect the accuracy of ambulatory recordings, such as arm movement, exercise, arm position, cuff or cloth friction. All these factors should be listed by the manufacturer.

In patients with cardiac arrhythmias, it is difficult and sometimes impossible to obtain an accurate measurement of blood pressure with a standard mercury sphygmomanometer. In these subjects the likelihood of obtaining an accurate ambulatory record is remote, and unless sound validation of accuracy is available for arrhythmias it should be assumed that ambulatory devices are probably inaccurate in these patients. The manufacturer's literature should carry a statement along the following lines: 'This instrument has not been validated in patients with arrhythmias'.

**Operator training requirement** Some ambulatory systems require considerable expertise on the part of the operator if accurate measurements are to be obtained, whereas other systems require relatively little instruction. These requirements should be stated.

**Computer analysis** Some ambulatory systems are compatible with personal computer systems. The exact requirements for linking with computer systems and their cost should be stated. If the ambulatory system is dependent on its own computer for plotting and analysis this should be made clear and the cost of the computer facility, if it is an optional extra, should be stated.

Clear instructions should be provided for setting recording conditions (e.g., frequency of recordings during defined periods, on/off condition of digital display); retrieving recordings and saving data to disk; retrieving data from disk; displaying numerical data and graphics; importing data into statistical/graphics/spreadsheet software programs; printing results (excerpts or total).

The manufacturer should list compatible computers (PC or other) and printers together with memory requirements, compatible graphic adaptors, additional software or hardware requirements (including interfaces and cables if these are not supplied).

**Problem list and solutions** Finally, a list of common operational problems should be listed with the means of detection and remedy.
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