

Task Force I: Methodological aspects

Criteria for validation of devices

Eoin O'Brien, Blood Pressure Unit, Beaumont Hospital, Dublin, Ireland

The patient of the population? The paradox of validation protocols

Thomas G. Pickering, Hypertension Center, New York Hospital–Cornell Medical Center, New York, USA

Frequency of measurements

Gert A. van Montfrans, Department of Internal Medicine, Academic Medical Centre, University of Amsterdam, The Netherlands

Editing recordings

Marco Di Rienzo, Centro di Bioingegneria, Fnd Don C Gnocchi and Politecnico di Milano, Milan, Italy

Methods of analysis

Eoin O'Brien, Blood Pressure Unit, Beaumont Hospital, Dublin, Ireland

Definitions of daytime and night-time blood pressures

Robert Fagard, Katholieke Universiteit Leuven, Hypertensie en Cardiovasculaire Revalidatie Eenheid, Inwendige Geneeskunde–Cardiologie, U.Z. Gasthuisberg, Leuven, Belgium

Variability of intermittent recordings

Thomas G. Pickering, Hypertension Center, New York Hospital–Cornell Medical Center, New York, USA.
Blood Press Monit 4:279–293 © 1999 Lippincott Williams & Wilkins.

Blood Pressure Monitoring 1999, 4:279–293

Keywords: device validation, AAMI, BHS, measurement frequency, data analysis, editing, variability

Received 6 October 1999 **Accepted** 22 October 1999

Criteria for validation of devices Data from 19 validation studies has been analysed to show that the British Hypertension Society/Association for the Advancement of Medical Instrumentation protocols can be unified and greatly simplified without compromising the validity of results by implementing the following measures: eliminating the

calibration and in-use phases; relaxing the ranges of blood pressures required; reducing the number of subjects from 85 to 33; assessing results in a primary phase in order to dismiss 'hopeless' devices after validation with 11 subjects; and using validation aids, such as audio-visual recording of comparative measurements.

The patient or the population? The paradox of validation protocols

There is a fundamental paradox in the design of current validation protocols for testing blood pressure monitors. The procedures are designed to answer the question of whether a given monitor will, on average, give valid readings for a population, but what we want to know in practice is the probability that the monitor will give accurate readings for a particular patient. The above considerations make it clear that, with the current criteria of acceptability and method of analysis, there will be a sizable number of individual subjects for whom any given monitor will not be validated to within 5 mmHg. The implications of this for validation studies and the means of addressing the problem are discussed.

Frequency of measurements in intermittent

ambulatory blood pressure monitoring (ABPM) Various approaches to deciding how frequently intermittent measurements should be made are examined. It is concluded that the number of measurements performed during 24 h ABPM clearly should not be less than one every 30 min, both for the day and for the night. When precision is of utmost importance, the sampling rate can be increased. A full diurnal curve is not always required in order to address individual clinical problems, so recording during the night can sometimes be omitted. Shorter recordings in the clinic offer a welcome substitute for many routine situations, but backing up with full 24 h ABPM when a short segment exhibits no hypertension seems mandatory, when important clinical decisions, such as withdrawing treatment, are dependent on the result.

Editing of ABPM data The definition of the criteria for editing series of blood pressure parameters derived intermittently from ABPM proposed on the base of the experience accumulated over the years in the leading centres in the field. Strict application of these criteria may be applied to give rigorous editing of data, which may be dependent on several factors, including the number of available measurements, the quality and reliability of the measuring device and the aim of monitoring.

Methods of analysis There are more than 40 ABPM systems on the market. Each of these has its own method for analysing 24 h data and for plotting the data. This often leads

to confusion on comparing the data and particularly on comparing one 24 h plot with another. There is a case, therefore, for the standardization of ABPM analysis and plotting so that the plot and data should be readily recognizable by the user, regardless of the device used, as is the case, for example, with electrocardiographic recordings. A computer program, DABL2000, provides the facility for simple or sophisticated analyses depending on the requirements of the user, a standardized method of plotting the data and the capability of providing a computer-generated report of the ABPM plot.

Definitions of daytime and night-time blood pressures

There is at present no consensus concerning the definitions of daytime and night-time blood pressures and at least 10 different methods have been employed. The techniques can be divided into clock-time-independent and clock-time-dependent methods and, in addition, into 'wide' methods, which use all blood pressure measurements throughout the 24 h period, and 'narrow' methods, which exclude part of the measurements. The awake or out-of-bed and asleep or in-bed blood pressures are usually considered as the optimal standards for daytime and night-time blood pressures, to which other definitions are compared. The narrow clock-time-dependent method, with a request to the subject to observe the transition periods, provides the optimal definition of daytime and night-time blood pressures.

Variability of intermittent ABPM recordings

Conventional ABPM using discontinuous readings taken every 15 min or so can give only a crude estimate of variability of blood pressure and will clearly provide no useful information about short-term changes. Variability of blood pressure is reviewed in terms of a number of rhythms with a characteristic periodicity, which may be intrinsically or extrinsically determined, on which are superimposed extrinsic influences and a certain amount of random error. One of the problems with estimates of variability of blood pressure such as the SD obtained from ABPM is that they have a low test-re-test reliability. This may be improved by standardizing activity on the two occasions and applying the method involving the root of the mean squared successive differences.

Criteria for validation of devices

Eoin O'Brien

Introduction

Experience with the protocols of the British Hypertension Society (BHS) [1] and the Association for the Advancement of Medical Instrumentation (AAMI) [2] has provided valuable insight into the methodological problems associated with device validation. The two protocols have many similarities, but there are some important differences

[3–8]. The protocols have been reconciled previously [9]. The differences between the protocols merit consideration to facilitate manufacturers' seeking to validate devices for acceptance both in Europe and in the USA. One of the objectives of the working group of the European Society of Hypertension is to investigate the possibility of having a common protocol, which would be accepted as the international standard for the validation of devices for measuring blood pressure [10]. In an attempt to unify the two protocols and to simplify the validation procedures, data from 19 device-validation studies performed in the blood pressure unit in Dublin have been analyzed to determine how the results would have been affected by smaller samples and alterations of recruitment ranges [11].

Simplification of BHS/AAMI validation procedure

The quest for harmonization and simplification of the two protocols can be concentrated on the following areas.

Elimination of pre-validation phases

The BHS protocol is divided into two parts [1]. Part I comprises the main validation procedure and has five phases: before-use calibration of a device; in-use (field) phase; after-use calibration of a device; static validation of a device; and reporting results of evaluation [9]. Part II of the BHS protocol consists of validation procedures for special groups and circumstances: pregnancy, the elderly, children, during exercise and various postures. Part II is performed only if the device obtains grade A or B during part I of the validation. Assuming that all devices for self-measurement have fulfilled the necessary requirements to obtain a EU certificate, it is not necessary to subject these devices to the first three phases of the BHS protocol.

Improving observation methodology

The most fallible component of blood pressure measurement is the human observer. The traditional technique of measuring blood pressure does not allow the result of the measurement to be checked by independent observers, thereby leaving the method open to bias. Another major difficulty with the BHS protocol has been in training observers and ensuring that they remain in agreement for the period of the validation study. The Sphygmocorder, a system in which the traditional method of measuring blood pressure has been combined with audio-visual recording technology to provide recorded data of the comparative measurements, overcomes these difficulties and removes the expensive need to employ observers throughout the validation procedure [12]. The Sphygmocorder has been

Table 1 Primary-phase requirements: 15 subjects

| | Comparisons must reach at least one of the following | | |
|--------------|--|-----------|-----------|
| | ≤ 5 mmHg | ≤ 10 mmHg | ≤ 15 mmHg |
| Simultaneous | 25 | 35 | 40 |
| Sequential | 20 | 30 | 35 |

Table 2 Secondary-phase requirements: 33 subjects

| | 99 Comparisons must reach at least two of the following | | | 99 Comparisons must reach all of the following | | |
|--------------|---|-----------|-----------|--|-----------|-----------|
| | ≤ 5 mmHg | ≤ 10 mmHg | ≤ 15 mmHg | ≤ 5 mmHg | ≤ 10 mmHg | ≤ 15 mmHg |
| Simultaneous | 60 | 85 | 95 | 60 | 80 | 90 |
| Sequential | 50 | 75 | 90 | 45 | 70 | 85 |

Table 3 Range requirements for primary phase (five subjects in each category) and secondary phase (11 subjects in each category)

| | Blood pressure (mmHg) | | |
|-----|-----------------------|---------|-------|
| | Low | Medium | High |
| SBP | < 130 | 130–160 | > 160 |
| DBP | < 60 | 80–100 | > 100 |

SBP, systolic blood pressure; DBP, diastolic blood pressure

validated for accuracy against the trained human observer using the protocol of the BHS [12].

It is recognized, of course, that not all validation centres will have the Sphygmocorder and, where observers are being used, the protocol must take into account the role of education and certification of observers. Two developments towards this end are to be welcomed. First, two CD-ROM are available for training and assessing observers [13,14]. Second, Colson Ltd has developed an observer kit with two connected observer stations, each with a mercury column, a steady-deflation mechanism and a recording facility.

Reduction in numbers

Reducing the number of subjects required for validation would simplify the procedure greatly and there are now sufficient data from the many validation studies performed to allow a review of the number of subjects required [11]. The use of simulators to augment the comparative measurements also shows promise as a means of reducing the number of hypertensive subjects presently demanded by the protocols, but simulators themselves will have to be validated before they can substitute for human subjects [15].

Both the AAMI and BHS protocols require a sample size of 85 subjects with three pairs of measurements each. Original power calculations were based on 85 pairs of measurements, which did not allow for the fact that the sample size required to prove the accuracy of a difference decreases as that difference increases, which means that a smaller sample is required to prove that a device is very inaccurate than is required to prove that a device is accurate. Our data support dividing the validation process into two phases: a primary phase in which three pairs of measurements are performed with 15 subjects and a device failing this phase (Table 1) is eliminated from further testing, whereas one passing it proceeds to a secondary phase, in which a further

18 subjects (in total 33) are recruited, for whom comparisons must fulfil the criteria shown in Table 2. These alterations did not substantially alter the results of any of our studies, but they would have greatly simplified the validation process [11].

Range of blood pressures

Experience has shown that recruiting subjects at the extremes of high and low blood pressures is impractical. Furthermore, because variability of blood pressure is greater at these extremes, sequential comparisons are often unreliable. The relaxation of these requirements to those shown in Table 3 with an equal number of subjects being recruited to each range facilitates the validation procedure without unduly affecting results [11].

Improving analysis of data

The data from a modified (simplified) validation procedure based on the above will need to be analysed. The software program devised by De Gaudemaris is ideal for such a purpose, in that it not only performs a full statistical analysis but also plots the data according to the recommended criteria [16].

Conclusion

If the above modifications can be incorporated in a collaborative revision of the BHS and AAMI protocols, the process of validation will be greatly facilitated. The benefit of such a protocol would be threefold: more centres could perform validation studies; more devices would thereby be validated; and European and American criteria for validation would be satisfied, thereby giving the protocol more international applicability than has been possible so far.

The patient or the population? The paradox of validation protocols

Thomas Pickering

Introduction

There is a fundamental paradox in the design of current validation protocols for testing blood pressure monitors. The procedures are designed to answer the question of whether a given monitor will, on average, give valid readings for a population, but what we want to know in practice is the probability that the monitor will give accurate readings for a particular patient. The answers to the two

questions are not necessarily the same. The criteria that a monitor must satisfy both for the protocol of the British Hypertension Society [1] and for that of the Association for the Advancement of Medical Instrumentation (AAMI) [2] are based on pooled data from the population sampled; the criteria for the latter are a mean systematic error between the monitor and a mercury sphygmomanometer within ± 5 mmHg and a SD of the individual validation readings within 8 mmHg. Under the assumption that the errors of the individual validation readings are normally distributed around the mean error, it can be shown that, for a monitor that satisfies the AAMI criteria with a mean error of ± 5 mmHg and SD of 8 mmHg, only 39% of the individual readings that resulted in the 'satisfactory' rating will have been within the ± 5 mmHg range that we would consider acceptable. Similarly, a monitor with a mean error of 3 mmHg and a SD of 5 mmHg should still have only 65% of individual readings within the ± 5 mmHg range. The conventional way of displaying the individual error points on the Bland-Altman plots confirms that there are many individual readings outside the ± 5 mmHg range for most of the published validation studies, but does not identify how these errors are distributed for the individual subjects. However, when the individual subjects' data are analysed, it is apparent that the errors for any one subject tend to be clustered and that the mean error for one subject is not the same as the mean error for the population. In fact, approximately one-third of subjects whose data were recorded by a monitor that satisfies both the British Hypertension Society and AAMI criteria are found to have a mean error exceeding ± 5 mmHg (data from [17]).

Conclusions

The above considerations make it clear that, with the current criteria of acceptability and method of analysis, there will be a sizable number of individual subjects for whom any given monitor will not be validated to within 5 mmHg. What can we do about this? There are at least three possibilities.

First, we could set more stringent criteria for acceptability. On theoretical grounds, we can show that, if, for example, we demand a mean error of 2 mmHg or less, with a SD no greater than 4 mmHg, the proportion of readings within our desired range (± 5 mmHg) would still be only 73%. There is a practical limit to how stringent we can make the criteria, however.

Second, we could change the analytical methods. We could specify that there should be no screening of subjects on the basis of the ease of detection of their blood pressure readings before testing and analyse according to the individual as well as the population.

Third, we could emphasize that every monitor needs to be tested on every patient. This would mean developing a

mini-protocol that could be used by clinicians in everyday practice.

There are other considerations as well. First, the implications for the error of using simultaneous rather than sequential readings need to be taken into account. Second, there has been virtually no research on individual differences in validation studies. For example, if a monitor fails to be validated for one subject on one occasion, what is the reproducibility of this? Will other similar monitors also fail? What are the characteristics of subjects that result in poor validation?

Frequency of measurements in intermittent ambulatory blood pressure monitoring

Gert A. van Montfrans

Introduction

Ambulatory blood pressure measurement reduces variability of blood pressure in comparison with that for conventional single measurements in the office by providing numerous measurements over a short time and so increases reproducibility. The obvious question of just how many readings are needed to obtain the best possible estimate of the prevailing pressure has been addressed by several authors in various ways. First, the relation of the duration of the interval between consecutive readings and the accuracy of estimating the full 24 h average was investigated. Accuracy was expressed first as the difference between the mean of a limited number of readings and that of a grand total provided either by continuous intra-arterial recording or by frequent intermittent ambulatory blood pressure monitoring (ABPM) and second as the dispersion of individual values around the mean obtained by taking a limited number of point estimates of blood pressure compared with that for very frequent sampling. Second, more specifically the shape of the diurnal curve and the reproducibility of short segments of the 24 h curve were assessed in relation to the sampling rate. Third, some authors sought to translate the benefit of ABPM over incidental office readings into practical terms, by assessing the relation between reproducibility and number of measurements in terms of changes in statistical power. Studies from the patients' perspective, for example concerning willingness to be subjected to a repeat study as a function of the number of readings during the first recording, do not seem to have been performed, although a large survey on acceptability of ABPM might contain the relevant data [18]. The conclusions that end this brief review re-affirm most aspects of current practice, but also it is recommended that one repeats the collection of whole 24 h records in order to increase specificity, when clinical decisions really matter.

Interval and accuracy of the full 24 h curve

The very first fully automated intermittent recordings used to be taken at 15 min intervals, which duration was probably selected as a trade-off between obtaining as many readings for plotting the diurnal curve as were acceptable for subjects who were supposed to 'follow their normal daily routine' [19]. More than 16 years ago Di Rienzo *et al.* [20] recorded complete sets of continuous 24 h intra-arterial data and compared those with single-blood-pressure waves of the same recordings at intervals of 5, 10, 15, 30 and 60 min. For each of 20 subjects the intermittent measurements at intervals of 5, 10, 15 and 30 min provided a zero-to-minimal difference from the reference blood pressure. Average values of the single-blood-pressure waves were often identical to those provided by the continuous measurements in which all waveforms recorded throughout the 24 h were included (differences were 1 mmHg or less). For the samples taken at 60 min intervals these differences were still no more than 2–3 mmHg. However, this did not hold for the SD. For the intervals of 5, 10 and 15 min differences amounted to $\pm 10\%$ of the SD of the grand total exceeding 100 000 beats. Intermittent recording of blood pressure (which operates best when readings are taken with subjects motionless) clearly does not allow one to appreciate the full extent of variability of blood pressure, but gives a precise estimate of the 24 h average with readings every 30 min. Similar data were obtained in another study using intermittent non-invasive and continuous intra-arterial recording, that also took into account reproducibility over a 4-week interval [21]. The SD of the difference between the 24 h averages, both for the intermittent and for continuously measured groups, decreased by 59% for systolic and 42% for diastolic blood pressure when the number of measurements analysed was increased from two to 24. No further fall was seen when more than 24 values were considered for both groups. The difference between mean values of blood pressure in the two recordings was hardly influenced by the sampling rates for the two groups.

Palatini *et al.* [22] analysed the reproducibility of 24 h blood pressures taken twice in 3 months for 508 hypertensive patients in the HARVEST. Measurements were taken at intervals of 10 min during the day and 30 min at night. Analysis using a halved sampling rate caused only a small drop in reproducibility, both of the averages and of variability. This was in line with the modest sampling rates that were recommended by authors of the studies mentioned above. However, recent data on the same cohort lead one to stress the importance of allowing only reproducible full 24 h recordings to guide making of clinical decisions [23]. When the differences in 24 h blood pressure exceeded 4 mmHg systolic or 3 mmHg diastolic between the two ABPM sessions, as was the case for a substantial number of subjects, correlations to indices of organ damage were no longer better than those for office blood pressure.

Interval and the diurnal curve

Together with the increasing interest in the clinical relevance of the diurnal profile of blood pressure, methodology for how best to analyse the circadian variation without loss of accuracy was proposed. There is no shortage of statistical papers discussing the various methods [24], but a detailed analysis of the optimal number of measurements combining accurate assessment of the average level of blood pressure with that of the drop in blood pressure at night and some other measures of the diurnal profile was published by Thijs *et al.* [25]. Single 24 h recordings for 97 normotensive subjects were obtained with measuring intervals of 7.5 min during the day (0800–2000 h) and 15 min at night. These recordings served as a reference. Five different sampling rates were analysed: of 15 and 15, 15 and 30, 30 and 30, 30 and 60 and 60 and 60 min for day and night-time intervals, respectively. In contrast to the minimal impact of the sampling rate on the estimation of the level of blood pressure, the effects on the various parameters of the diurnal profile such as 24 h SD, nocturnal fall in blood pressure and the amplitude of the Fourier curve were more pronounced and gradually increased with decreasing sampling frequency. In terms of these criteria, a minimum of one measurement every 30 min both during the day and during the night seems an acceptable compromise between accuracy and acceptability for routine clinical practice. Expanding this kind of analysis to a between-ABPM reproducibility study, also including subjects with higher blood pressures, would be interesting, since variability of blood pressure increases with increasing blood pressure.

Shorter periods

Again, authors of the first article on this subject used intra-arterial continuous recordings as the frame of reference [26]. Sub-periods averaged over 30 min and 1, 2, 4, 8 and 12 h were compared with individual daytime and 24 h values for 40 subjects. Short-time differences from 24 h averages for the whole group 'were frequently small' but individual differences exhibited a large scatter and this also applied for short periods of daytime compared with the whole-day average, removing the bimodality of rest versus activity. With intermittent readings obtained in a strictly standardized fashion, thus avoiding the large inherent variability of continuous measurement, however, reproducibility of short-time 3 min readings was quite acceptable and in fact similar to the reproducibility of the average 24 h blood pressure obtained by ABPM. In that study the SD of the differences fell progressively during the initial readings and then more slowly until 25 measurements had been made [27]. When variability is larger, such as for the elderly hypertensive patient, longer 'short' periods may be needed in order to achieve reasonable accuracy [28]. More studies of this type, comparing short-term registrations with a full data set, were discussed by Sheps *et al.* [29] and Braun *et al.* [30]. The latter emphasizes the importance of using the same type of device when the biological variability of blood

pressure is being evaluated; clearly, one does not want to add further noise to variability of blood pressure by using different devices, each with its own technical peculiarities.

Short-term recording of course is attractive and convenient, but the chances of misclassification cannot easily be ascertained from the available data. Braun *et al.* classified 25% of hypertensive subjects wrongly as having office hypertension, on the basis of comparisons between conventional sphygmomanometry and the SpaceLabs device. When important decisions regarding treatment depend on it, verification by performing a full 24 h recording seems appropriate, just as is being recommended for self-recording of blood pressure.

Interval and sample size

Coats *et al.* [31] were the first to translate the better reproducibility of ABPM versus conventional office readings into clinical trial management [31]. They demonstrated that the SD of the differences between duplicate estimates of the diastolic blood pressure decreased from 12.3 mmHg for a single reading to 6.3 mmHg for the average of at least 20 readings of the daytime ambulatory blood pressure. Halving of the SD of the difference in blood pressure between two measurements results in decreasing the required sample size by 75% in a cross-over trial. These findings were based on a reproducibility study concerning 100 subjects aged 18–72 years with mild-to-moderate hypertension. Assuming that these variabilities also applied to parallel-group studies, the authors proposed that, in order to detect a difference of 5 mmHg for diastolic ambulatory blood pressure with a power of 80%, sample size in a group-comparison study could be reduced from 250 to 67 subjects. However, considering the sample size for parallel groups, these recommendations appeared too optimistic and are certainly less generalizable than was hoped. Staessen *et al.* [32] convincingly showed for a sample from the placebo-controlled Syst-Eur study on elderly subjects with isolated systolic hypertension, in which two 24 h recordings were performed with 1 year in between that, both for clinic data and for ABPM, 40 subjects in each group (not 33) were needed in order to detect a difference in diastolic 24 h blood pressure of 5 mmHg caused by treatment. These findings were not surprising, the authors commented, since the between-subject rather than the within-subject variability determines the test statistic for calculating power in parallel-group studies. Thus, the general view is that, when one is using ABPM, at least in parallel-group studies, one should not economize on sample size. In the same article it was also shown that, in order to detect stability of reduction in blood pressure throughout the 24 h, one needs stable hourly reductions, calling for more rather than fewer patients versus calculations based on clinic readings. Indeed, hourly reproducibility of blood pressure is much more variable than are whole-day or 24 h averages [33].

Conclusions

The number of measurements clearly should not be less than one every 30 min, both for the day and for the night. When precision is of utmost importance, the sampling rate can be increased in daytime to once every 20 or 15 min for example. A full diurnal curve is not always required in order to address individual clinical problems, so recording during the night can sometimes be omitted. Shorter recordings in the clinic offer a welcome substitute for many routine situations, but backing them up with a full 24 h recording when a short segment exhibits no hypertension seems mandatory, when important clinical decisions, such as on withdrawing treatment, are dependent on the result. Likewise, a second 24 h recording should be considered in these cases in order to obtain maximum accuracy.

Editing of ambulatory blood pressure monitoring recordings

Marco Di Rienzo

Introduction

At present the vast majority of the non-invasive 24 h ambulatory blood pressure monitorings (ABPM) performed for clinical purposes are based on use of devices that measure blood pressure in an intermittent fashion through the automatic implementation of the traditional Korotkoff or oscillometric technique. This article will be focused on the definition of the criteria for editing series of blood-pressure-derived parameters [usually systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure and heart rate] provided by these devices.

The editing procedure

The editing procedure is intended to identify and remove the artefacts that possibly are present in the ABPM data. As a general statement, the maximal accuracy in data identification of artefacts can be expected when the checking of the blood-pressure-derived parameters is combined with the inspection of the signals from which the parameters are estimated (i.e. the Korotkoff sounds in the case of microphonic devices and the oscillometric signal for the oscillometric devices). In most instances, however, these signals are not made available to the user and the blood-pressure-derived parameters are the only information supplied by the monitoring device. In this case the correct detection of the artefacts becomes a troublesome task and misclassification errors are likely to occur. In fact, when only the blood-pressure-derived parameters are provided, an artefact can be identified with certainty if the value of one or more parameters derived from a given automatic measurement is clearly outside the physiological range or if the value of one parameter is not congruent with those of

the other parameters derived from the same measurement (e.g. DBP value > SBP value). Apart these 'macroscopic' artefacts which are, or should be, automatically detected and removed by the built-in software that controls the measuring device, we are left with the remaining 'milder' artefacts which escape automatic built-in removal procedures and produce derived parameters that deviate only marginally from values commonly seen in a clinical setting. The correct identification of these 'milder' artefacts is obviously more difficult and multi-step editing procedures are required in order to minimize the chance of errors (i.e. that a correct measurement is incorrectly classified as an artefact or vice-versa). Usually, for each blood pressure measurement, the value of each parameter is first compared with a threshold value to verify whether it is within the physiological range and then is subjected to further controls, including checking the congruence of the value concerned with the value of the other parameters derived from the same measurement (e.g. SBP versus DBP, SBP or DBP versus heart rate), checking the congruence between the observed values and the information provided by the patient in his/her diary and evaluating the context (e.g. paying attention to the acceptance of an isolated 'apparently good' value when it is interspersed among several contiguous discarded measurements).

In Table 4 are shown the editing criteria proposed by the consensus committee, on the basis of the experience collected over the years by the leading investigators working in the field and of the guidelines emanating from the Italian Society of Hypertension [34]. It is apparent that, with the exception of the thresholds, most of the other criteria are in part qualitative and can thus be applied in a more or less strict way according to specific needs. A strict application of these criteria will obviously result in stringent editing of the data. This approach increases the chance of eliminating 'true' artefacts but with some risk of deleting 'good' values, too. Thus, the quality of the monitoring is enhanced at the possible cost of an excessive pruning of the original data set. In contrast, a 'weak' application of the criteria will tend to preserve as many values as possible at the cost of a less effective elimination of artefacts.

The selection of the proper level of stringency of the editing procedure to be performed depends on several interdependent factors (see also Table 5).

The number of measurements performed over the 24 h A large number of measurements in the original data set will give us the possibility to use a more stringent strategy in the editing phase in case of quality of the monitoring. The original number of measurements obviously depends on the time intervals between assessments of blood pressure. By programming an automatic measurement of blood pressure every 15 min during the daytime and every 20–30 min

during night-time, as is usually done, we can rely on obtaining about 85–100 readings per monitoring.

The quality and reliability of the measuring device High quality of the measurements and reliability of the built-in algorithms for noise rejection reduce the need for stringent editing. It should be emphasized, however, that, although the assessment of the quality of the single reading is feasible (by comparing the results obtained by the system being tested with those simultaneously obtained by another validated system), the built-in algorithms for noise rejection are commonly not disclosed and therefore their evaluation can hardly be performed by investigators independently of the company which produces the device.

The aim of the monitoring The quantity to be estimated as a final objective of the ABPM (e.g. the mean value, SD, circadian rhythm, day–night change, etc.) is the most important factor in determining the editing strategy. For example, if the goal of a study is the assessment of the 24 h mean value, a number of samples as low as one every 30 min is sufficient, but it is important that the available samples be evenly distributed over time. Conversely, if the aim is the evaluation of the 24 h SD, the number of values accepted becomes important and at least one sample every 10 min is required [20,35–37]. If the blood-pressure characteristics for specific time periods (e.g. during the peak and trough times for the assessment of the effects of an antihypertensive drug) are to be evaluated, it is important to guarantee that one will obtain an appropriate number of samples concentrated in the periods of interest. Thus each quantity to be evaluated has its own requirements in terms of a minimal number of blood-pressure samples and their distribution over time in order for it to be reliably estimated. A few words to clarify this statement are required. The SBP, DBP, mean arterial pressure and heart rate values are parameters characterizing each heartbeat. Their intermittent assessment by traditional devices plus the further pruning due to the editing procedure unavoidably results in an aliasing error in the final data set [38]. The error due to the under-sampling becomes progressively greater as the number of available samples decreases and its practical impact on the final results depends on the quantity being investigated. For a number of quantities that can potentially be derived from the analysis of 24 h ABPM data, quantification of the impact of the aliasing error has never been performed and thus one should exercise caution in estimating these quantities from intermittent measurements before reliable data on their accuracy become available. It should be emphasized also that the under-sampling not only can reduce the accuracy of the results but also, in some instances, might even totally prevent one obtaining an accurate estimate of specific quantities. This seems to be particularly the case for the spectral estimation of the slower components of 24 h variability of blood pressure from intermittent readings of blood pressure. In fact, it has

Table 4 Editing criteria

First step based on the analysis of the signals from which the extracted parameters are derived (if these signals are available)
 Visual inspection of the microphonic or oscillometric signal, or both, and removal of measurements associated with abnormal signals

Second step based on the analysis of derived parameters

Measurements are discarded if they meet the following criteria

Criteria based on thresholds

Pulse pressure > 150 or < 10 mmHg

Systolic blood pressure > 300 or < 50 mmHg

Diastolic blood pressure > 150 or < 40 mmHg

Heart rate > 150 or < 40 beats/min (without explanation in patient's diary)

Criteria based on the reciprocal relationship between parameters

E.g. diastolic > systolic blood pressure

Criteria based on changes of each parameter over time

E.g. sudden and marked (> 30%) increases or reductions in blood pressure or heart rate, or both, compared with preceding values (without explanation in patient's diary)

Criteria based on the congruence with the patient's diary

Criteria based on the context

E.g. particular attention should be paid to accepting isolated 'apparently good' values if they are interspersed among several contiguous discarded measurements

been observed that, when fluctuations in blood pressure over the 24 h are evaluated by Fourier analysis with four harmonics, through the analysis of unevenly distributed and relatively few blood-pressure samples, such as those commonly provided by traditional ABPM devices, the resulting spectrum is significantly different from that derived for the same subjects by the analysis of the continuous intra-arterial blood pressure recorded simultaneously (G. Parati and S. Omboni, unpublished data).

Table 5 Factors to be considered for the selection of the appropriate level of stringency in the editing procedure

Number of measurements performed over the 24 h

The larger the number of available measurements the greater the possible stringency of the editing strategy

The number of measurements depends on the interval between samples programmed on the system. If the intervals one measurement every 15 min during daytime and one measurement every 20–30 min during night-time are selected, then about 85–100 readings per day will be available

Quality and reliability of the measuring device

High-quality measurements and reliable built-in algorithms for the detection and rejection of artefacts reduce the need for stringent editing strategies

Target quantity to be estimated

The most important factor in determining the editing strategy is the quantity to be assessed (e.g. the 24 h mean value, the 24 h SD, circadian rhythm parameters, day–night change, etc.), since each quantity has a specific requirement in terms of a minimal number of samples and their distribution over time in order for it to be reliably estimated. Once an acceptable level of signal quality has been attained, the editing strategy should be selected in order to satisfy the minimal requirements for the estimation of the quantity desired (Note: at present these minimal requirements are not available for every quantity that can be potentially derived from ambulatory monitoring data)

From the foregoing, it is clear that the stringency of the editing procedure should be such as to obtain a trade-off between proper suppression of artefacts, which is required for obtaining data of an adequate quality, and the need to keep a sufficiently large number of measurements to allow correct estimation of the quantity being investigated.

Methods of analysis

E. O'Brien

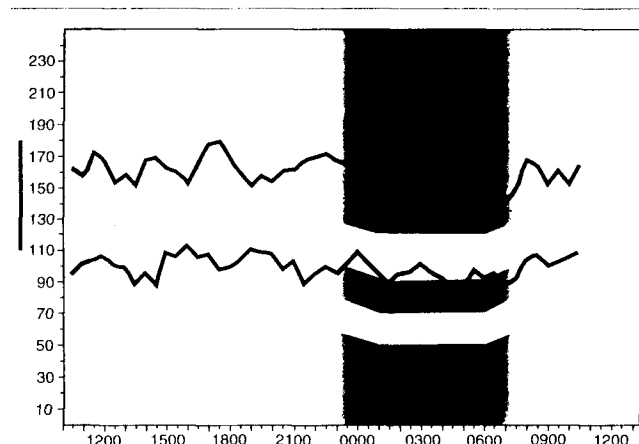
There are more than 40 systems for ambulatory blood pressure monitoring (ABPM) on the market [39]. Each of these has its own method for analysing 24 h data and for plotting the data. This often leads to confusion on comparing the data and particularly comparing one 24 h plot with another. Moreover, the software programs for this facility are often very expensive. There is a case, therefore, for the standardization of analysis and plotting of ABPM data so that, regardless of the device used, the plot and data should be readily recognizable by the user, as is the case, for example, with electrocardiographic recordings. A computer program, DABL2000, which has been developed in the blood pressure unit at Beaumont Hospital, has a number of attractive features, including the facility for simple or sophisticated analyses, depending on the requirements of the user, a standardized method of plotting the data and the capability of providing a computer-generated report of the ABPM plot [40,41]. The program can also provide a broad cardiovascular profile of risk.

The DABL2000 program

DABL2000 is a modular medical data-base system for the management of cardiovascular illness, which includes modules suitable for concentrating on one or more aspects of cardiovascular disorders, such as hypertension, dyslipidaemia and arterial disease. The program can store, retrieve and display an array of clinical and cardiovascular data, including ABPM data, concerning patients with hypertension and other cardiovascular illnesses.

The DABL system has been in use in the blood pressure unit of Beaumont Hospital for the past decade. DABL2000 is the eighth version of a series that has been developed over this time, evolving to suit the changing needs of contemporary clinical practice in cardiovascular medicine. The latest DABL2000 Windows version provides unique features to assist physicians in the diagnosis and management of hypertension and cardiovascular disease, which include automatic natural-language summaries, cardiovascular-event-risk indicators and a facility for determining whether goals of management of patients are being achieved.

Fig. 1



DABL2000 plot of 24 h ambulatory blood pressure: level of blood pressure is shown on the vertical axis, time of day on the horizontal axis (this time is adjusted automatically to commence at the time of initiation of a recording). Night-time is indicated by the darkly shaded area; the white-coat-hypertension window is depicted by the hatched area adjacent to the vertical axis; normal bands for systolic and diastolic blood pressures are depicted by the grey bands; office or clinic blood pressure is indicated by the vertical bar adjacent to the vertical axis and 24 h systolic and diastolic blood pressures are plotted. The computer-generated report reads 'Significant elevation of day and night-time systolic and diastolic blood pressures, with a non-dipping pattern for nocturnal diastolic pressure'.

DABL modules

DABL is designed in three modular forms; the first DABL Cardiovascular, contains all the requirements for making a complete cardiovascular assessment and for generating a report. The second, DABL Blood Pressure, allows incorporation of the DABL program's analysis and plotting schema for 24 h ambulatory blood pressure, or for home measurement of blood pressure. The third, DABL Research, completes the DABL system and allows comprehensive and elaborate statistical analyses to be performed on the DABL data base. This description will be confined to the blood pressure module.

Module II: DABL Blood Pressure

This module is designed for a more detailed assessment of blood pressure, facilitating the inclusion of home and ambulatory measurements of blood pressure. It contains comprehensive details of the patient's blood pressure. In particular, details from a series of readings from an ambulatory blood pressure monitor can be stored and displayed graphically or statistically. Ambulatory blood pressures are loaded directly from the monitor or from files generated by a manufacturer's software. They are stored and displayed in a format unique to DABL, whereby ABPM data are plotted in a standard format (Fig. 1), regardless of their source, against a background showing ranges of normality throughout day and night to facilitate diagnosis and comparison. Statistics are presented in basic or detailed

form for systolic and diastolic blood pressures, heart rate and mean arterial pressure for the initial hour, daytime, night-time and full 24 h periods. Basic statistics consist of mean, SD and load values, each of which is plotted for visual reference. In addition to these median, leese (excessive lowering of blood pressure), percentage load under curve, coefficient of variation, root mean square of successive deviations, number of load and leese events, duration of maximum load and leese events and empirical and percentage dip values are available in the detailed statistics. Durations of initial, daytime and night-time periods can be set individually. Bit maps of plots can be saved or copied to presentation software for case studies or for an ABPM library. Referral and office blood pressures are also analysed. Finally, the program will produce an overall indicator of severity of blood pressure and a natural-language report, which can be printed.

The data entered into this module can be studied for each patient individually or stored in a data base for future auditing and research. The Blood Pressure Unit, for example, has data on over 20 000 patients characterized in terms of risk and ambulatory blood pressure in its data base. DABL2000 is compatible with the major statistical packages such as SAS, SPSS and Excel. The program will generate either simple working statistics or more complex statistics for individual patients, or a more detailed analysis can be performed.

Definitions of daytime and night-time blood pressures

Robert Fagard

Introduction

There is at present no consensus concerning the definitions of daytime and night-time blood pressures and at least 10 different methods have been employed [42–44]. The techniques can be divided into clock-time-independent and clock-time-dependent methods and, in addition, into 'wide' methods, which use all pressure measurements throughout the 24 h period, and 'narrow' methods, which exclude some of the measurements. Modelling techniques that do not involve reporting averages of raw data, such as the cosinor method [45], Fourier analysis [46] and the periodic spline model [47], will not be discussed because they are unlikely to be introduced into clinical practice.

Definitions

Clock-time-independent methods

Awake and asleep blood pressure

The most obvious, meaningful and scientifically sound method for defining daytime and night-time blood

pressures would be to calculate the blood pressures for periods during which subjects are awake and asleep. Delineations of daytime and night-time are usually based on the times that subjects go to bed at night and get out of bed in the morning [44,48–53]. Other techniques such as electroencephalography and use of activity monitors [54] have been used mainly for research purposes.

Disadvantages of using the out-of-bed (awake) and in-bed (asleep) periods are that existing data bases do not always include the relevant times, that errors in their reporting or registration may occur and that they add to the complexity of the methodology. In addition, reproducibility of the day and the night-time blood pressures will be reduced if subjects wake up or go to bed at different times on different days. Another disadvantage of using the times of going to bed and rising is that the periods during which subjects are awake during the night or take a nap or siesta during the day are not considered; the importance of taking this into account has been debated [50,55,56].

The diurnal variation is usually calculated as the difference between the awake and asleep blood pressures (or vice versa). It is expressed in absolute units of blood pressure or as the percentage difference. Occasionally the night-time : daytime ratio of blood pressure is used.

Square-wave method

Idema *et al.* [57] introduced the square-wave-fitting method to analyse the diurnal variation of blood pressure because inspection of 24 h profiles suggested that a model of blood pressure as two contiguous periods of constant high and low pressure, a so-called wave, would be appropriate. The problem of the original method [57], namely that one outlying pressure or a short period of only a few pressure data could be identified as the low-pressure or the high-pressure interval by the algorithm, could be overcome by the implementation of restrictions, that is that the high-pressure period had to last at least 10 h and the low-pressure period at least 6 h [52,58]. An insuperable disadvantage is that the method identifies periods of high and low blood pressure, which will coincide with the day and the night in most instances, except for reverse dippers, who constitute about 5% of the population [59]. Furthermore, the correspondence of the transition times to the in-bed and out-of-bed times is limited, particularly for subjects with small awake–asleep differences in blood pressure [52].

Cumulative-sum analysis

Stanton *et al.* [60] identified by means of calculating cumulative sums the mean blood pressures of the 6 h periods of highest (crest) and lowest (trough) pressure. The advantage claimed by the authors is the lack of dilutional errors when subjects exhibit phase shifts in their sleeping/awake or inactive/active periods, or when these periods vary in duration. However, the method shares the disadvantage of

the square-wave method, namely that it identifies a period of highest and a period of lowest blood pressure, which do not necessarily coincide with the day and the night. Furthermore, the 6 h crest period is relatively short but it can be prolonged to last as long as 10 h [52].

Clock-time-dependent methods

The wide approach

In the wide methods the full 24 h is covered and two times to calculate daytime and night-time blood pressures are defined (e.g. from 0700 to 2200 h for the day and from 2000 to 0700 h for the night [61]; several other time periods have been used [44,48–50,53,54]). A drawback of the wide approach is that the predefined times do not usually correspond to the awake and sleeping times and that the day and the night may contain variable parts of the awake and sleeping periods, which may lead to differences among and within individuals.

The narrow approach

The purpose of the narrow approach is to exclude the morning and evening transition periods, during which blood pressure changes rapidly, from the analysis of the diurnal profile. For example, daytime might last from 1000 to 2000 h and night-time from 0000 to 0600 h [52,62], but also other time periods have been used [49,51]. Subjects can easily be instructed to observe these time intervals so that they are up and about during the day and in bed during the night. An argument against the narrow approach is that not all available information is used for the analysis; however, all blood pressures measured are included in the 24 h average blood pressure, which should always be reported.

Comparison of daytime and night-time pressures with the awake and asleep pressures

Clock-time-dependent methods

The wide approach

Most authors found that the average daytime blood pressures from the wide fixed-time method was lower than the average awake blood pressure, but the differences were very small, not exceeding 2 mmHg (Table 6). Night-time blood pressure consistently overestimated the asleep blood pressure, the average deviations ranging from 1 to 6 mmHg for systolic blood pressure and from 1 to 4 mmHg for diastolic blood pressure in the various reports. Consequently, the day–night differences were consistently underestimated by the wide fixed-time methods, by 1–7 mmHg for systolic blood pressure and 1–6 mmHg for diastolic blood pressure. Divergences of the daytime and night-time blood pressures from the awake and asleep blood pressures result from the fact that the true out-of-bed and in-bed periods do not coincide with day and night timings that are fixed in advance [51–53].

The narrow approach

The average daytime blood pressure was equal to or within

1 mmHg of the awake blood pressure, the average night-time blood pressures did not deviate by more than 3/2 mmHg from the asleep blood pressures and the results for the day–night differences in blood pressure were similar [49,51,52,63] (Table 7). The results obtained with the narrow fixed-time method are therefore closer to the individualized blood pressures than are those from the wide fixed-time methods, particularly for the night and the day–night differences. This results from the fact that the majority of the population goes to bed and wakes up within the transition periods. However, deviations from the predefined time schedules may still cause potentially important deviations from the awake and asleep blood pressures [51,52].

Clock-time-independent methods

Square wave

For a population without reverse dippers, a modified square-wave method overestimated the systolic out-of-bed blood pressure by approximately 1 ± 1.5 mmHg (mean \pm SD) and the diastolic blood pressure by about 1.5 ± 2 mmHg [52]. The in-bed systolic blood pressure was underestimated by about 1 ± 1.7 mmHg, whereas there was no significant difference for diastolic blood pressure. The day–night differences were overestimated by approximately 2 ± 2 mmHg.

Cumulative-sum analysis

Stanton *et al.* [60] compared the results from the cumulative-sum analysis with those obtained with a narrow fixed-time method. As could have been expected, the 6 h period of highest blood pressure overestimated the 12 h daytime blood pressure (from 0900 to 2100 h), the difference being 5/3 mmHg. In contrast, the 6 h trough blood pressure was

only 2/1 mmHg lower than the 6 h night-time blood pressure (from 0100 to 0700 h). When the crest period was extended to 10 h, Fagard *et al.* [52] found that the resulting blood pressure overestimated the out-of-bed blood pressure by about 2.5 ± 2 mmHg; the 6 h trough was lower than the in-bed blood pressure by about 2 ± 1.5 mmHg. The cumulative-sum analysis yielded the largest day–night differences in blood pressure of all methods applied. It should be noted that samples in these studies did not include reverse dippers.

Reproducibility

Authors of the few studies that compared the reproducibilities of various methods for the analysis of the diurnal profile of blood pressure used the signed difference in pressure between duplicate monitorings to assess group reproducibility and used repeatability to assess individual variation. The reproducibilities of various daytime (awake, fixed-time, crest and square-wave high) and night-time (asleep, fixed-time, trough and square-wave low) average blood pressures and of their differences appear to be excellent, all deviations being within 2.5 mmHg [58,60,63].

Conclusions

The out-of-bed (awake) and in-bed (asleep) blood pressures are usually considered the optimal standard for daytime and night-time blood pressures, against which other definitions are compared. However, they may add to the complexity of the analysis and errors may occur in noting down the exact times of patients' going to bed and getting up. The major problem with fully automated clock-time-independent analytical methods, such as square-wave fitting and cumulative-sum analysis, is that they identify periods of highest and lowest blood pressures, which do not

Table 6 Systolic/diastolic daytime and night-time blood pressures and day–night differences in blood pressure according to out-of-bed (awake) and in-bed (asleep) periods and to wide fixed-time periods

| Reference | Times (h) | n | Daytime (mmHg) | | Night-time (mmHg) | | Day–night difference | |
|----------------------------------|------------|-----|----------------|------------|-------------------|------------|----------------------|-------------|
| | | | Awake | Fixed | Asleep | Fixed | Awake–asleep | Day–night |
| Hansen [49] | 0630; 2230 | | | | | | | |
| Normal subjects | | 33 | 125/75 | 123/74 | 107/59 | 111/62 | 86%/78% | 91%/84% |
| Diabetics | | 33 | 129/77 | 128/72 | 114/61 | 117/65 | 88%/80% | 92%/90% |
| Stewart [55] | 0700; 2000 | 319 | 145.7/89.2 | 146.9/89.9 | 126.7/74.2 | 133.0/78.6 | 12.9/16.6 | 8.8/12.3 |
| Hypertensives | 0700; 2200 | | | 145.8/89.5 | | 130.4/76.8 | | 10.5/14.1 |
| 0700; 0000 | | | | 145.0/88.7 | | 128.0/75.0 | | 11.7/15.1 |
| Gatzka [50] | 0600; 2200 | | | | | | | |
| Normotensives | | 45 | 126/76 | 125/76 | 108/60 | 112/62 | 17.6/16.4 | 13.2/13.3 |
| Borderline hypertensives | | 20 | 135/81 | 133/80 | 116/64 | 121/67 | 18.5/17.2 | 11.7/12.6 |
| Essential hypertensives | | 56 | 146/93 | 145/92 | 129/78 | 132/80 | 17.7/15.6 | 12.9/12.4 |
| Renal transplant recipients | | 45 | 137/88 | 137/88 | 129/79 | 130/80 | 8.6/9.2 | 6.5/8.1 |
| Peixoto Filho [45] | 0700; 2200 | 50 | 139/83 | 138/82 | 119/71 | 121/73 | 18/11 | 17/9 |
| Normotensives and hypertensives | 0700; 0000 | | | 138/82 | | 120/73 | | 17/9 |
| van Ittersum [52] | 0700; 2200 | 95 | 145.8/91.4 | 145.7/91.5 | 126.3/75.4 | 130.1/77.8 | 86.7%/82.5% | 89.2%/85.0% |
| Hypertensives | | | | | | | | |
| Fagard [53] | 0700; 2200 | | | | | | | |
| Normotensives | | 91 | 127.9/75.1 | 125.3/73.0 | 109.8/58.1 | 114.8/62.4 | 18.0/17.0 | 10.5/10.6 |
| Those with usual living patterns | | 47 | 127.2/74.2 | 126.0/73.2 | 110.1/57.6 | 112.0/59.3 | 17.1/16.5 | 14.1/13.9 |
| Gosse [54] | 0600; 2200 | 88 | 132/88 | 131/87 | 115/74 | 117/75 | | |
| Normotensives and hypertensives | | | | | | | | |

^aAll values are expressed as mmHg, unless indicated as percentages, where the night-time : daytime ratio of blood pressure is given.

Table 7 Daytime and night-time blood pressures and day-night differences in blood pressure according to the out-of-bed (awake) and in-bed (asleep) periods and to narrow fixed-time periods

| Reference | Times (h) | n | Daytime (mmHg) | | Night-time (mmHg) | | Day-night difference ^a | |
|----------------------------------|----------------------|-----|----------------|------------|-------------------|------------|-----------------------------------|-------------|
| | | | Awake | Fixed | Asleep | Fixed | Awake-asleep | Day-night |
| Gatzka [50] | 1000-2300; 0100-0700 | | | | | | | |
| Normotensives | | 45 | 126/76 | 127/77 | 108/60 | 109/61 | 17.6/16.4 | 17.7/15.9 |
| Borderline hypertensives | | 20 | 136/81 | 136/82 | 116/64 | 118/65 | 18.5/17.2 | 18.3/16.7 |
| Essential hypertensives | | 56 | 146/93 | 146/93 | 129/78 | 130/80 | 17.7/15.6 | 16.2/13.5 |
| Recipients of kidney transplants | | 45 | 137/88 | 137/88 | 129/79 | 130/80 | 8.6/9.2 | 7.1/7.2 |
| van Ittersum [52] | 1000-2300; 0100-0700 | 95 | 145.8/91.4 | 145.5/91 | 126.3/75.4 | 125.9/75.4 | 86.7%/82.5% | 87.7%/83.0% |
| Hypertensives | | | | | | | | |
| Fagard [53] | 1000-2000; 0000-0600 | | | | | | | |
| Normotensives | | 91 | 127.9/75.1 | 127.6/75.1 | 109.8/58.1 | 112.6/60.3 | 18.0/17.0 | 15.0/14.7 |
| Those with usual living patterns | | 47 | 127.2/74.2 | 127.8/74.7 | 110.1/57.6 | 109.7/57.0 | 17.0/16.5 | 18.1/17.7 |
| Staessen [64] | 1000-2000; 0000-0600 | | | | | | | |
| Hypertensives | | 169 | 154/85 | 154/85 | 136/71 | 136/71 | | |
| Hypertensives | | 168 | 153/84 | 154/84 | 136/70 | 137/70 | | |

^aAll values are expressed as mmHg, unless indicated as percentages, where night-time : daytime ratio of blood pressure is given.

necessarily coincide with the day and the night, for example for subjects with a reversed day-night pattern of blood pressure. Among the fixed-time methods, the wide methods, which cover the full 24 h include variable portions of the actual periods of patients being awake and asleep in the arbitrarily defined day and night-times, which might lead to important group and individual differences between the two approaches, particularly for the night-time blood pressure and the day-night difference in blood pressure. In addition, it is impractical to ask the subjects to go to bed and get up exactly at the predetermined times. Narrow clock-time-dependent methods reduce these problems and yield daytime and night-time blood pressures and day-night differences in blood pressure that are close to the out-of-bed and in-bed values, provided that the subjects go to bed and wake up within the predefined transition periods, which should not disrupt the usual living patterns of most people. It is likely that the duration of the transition periods and the simplicity of the method in general make it applicable to the majority of individuals in most populations, both for clinical purposes and for epidemiological surveys. We therefore suggest that the narrow clock-time-dependent method, with a request that the subject observe the transition periods, provides an optimal alternative definition of daytime and night-time blood pressures [66].

Variability of intermittent ambulatory-blood-pressure-monitoring recordings

Thomas G. Pickering

Introduction

The justification for ambulatory blood pressure monitoring (ABPM) is that blood pressure varies and a better understanding of the causes of such variability will greatly improve our knowledge of its consequences. In principle,

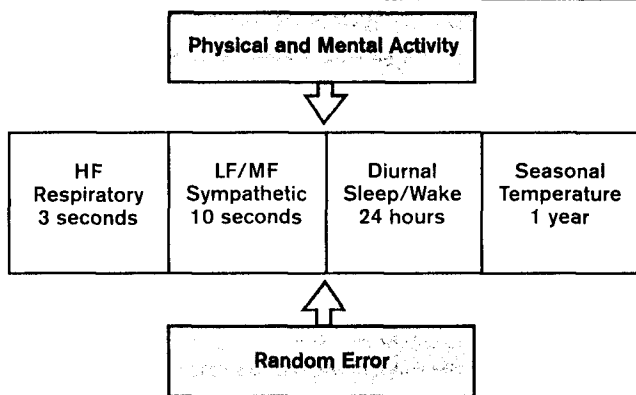
ABPM can provide information on three aspects of blood pressure: the average level, the diurnal rhythm and short-term variability. Although it is generally assumed that the average or true level of blood pressure is the main culprit causing vascular damage, it would be surprising if the variability did not also contribute. Variability of blood pressure is a complex issue and is the result of internal and external influences acting in various combinations. Conventional ABPM using discontinuous readings taken every 15 min or so can only give a crude estimate of variability of blood pressure and will clearly provide no useful information about short-term changes. Furthermore, it is customary to change the frequency of readings during the night, for example to take readings every 15 min during the day and every 30 min at night. If the interval between readings varies in this way, the level of blood pressure at night will be under-represented if the simple 24 h average is computed. Therefore, a time-weighted average level would be more appropriate.

ABPM is normally performed with free-ranging subjects, whose activities will almost certainly exhibit significant between-subject differences. If these differences are very large, they will introduce a significant bias into the overall mean level of blood pressure. A prime example of this would be comparison of data from one subject studied on a work day with data from another studied on a non-work day. This confounding factor is equally important for within-subject comparisons. An example of this would be a study assessing the effects of an antihypertensive medication, in which the same subjects are monitored with and without medication. Activity should as far as possible be held constant from one occasion to another, to minimize the potential confounding of the effects of the medication by variation of activity between occasions.

The major determinants of variability of blood pressure

Variability of blood pressure can be considered in terms of a number of rhythms with characteristic periodicities, which

Fig. 2



The major sources of blood pressure variability are shown. The open boxes show rhythmical sources of variability; HF, high frequency; MF, mid frequency; LF, low frequency.

may be intrinsically or extrinsically determined, on which are superimposed extrinsic influences and a certain amount of random error (Fig. 2). Intrinsic rhythms include those deriving from respiration, cyclical fluctuations in sympathetic nervous activity and diurnal rhythms. Extrinsic influences include the level of physical and mental arousal and seasonal changes.

Much of the variability of blood pressure in free-living people during the day can be attributed to the effects of activity, rather than to intrinsic rhythms. 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 10–20% occurring during sleep [67]. It has also been shown that diurnal changes in blood pressure in hospitalized patients are less pronounced than those in patients studied in their natural environments [68]. Both the average level of blood pressure and its variability are less during periods of rest in bed than they are during periods of physical activity [69]. These findings support the view that the diurnal rhythm of blood pressure is more dependent on the cycle of rest and activity than it is on the biological clock.

Posture and the effects of activity

Posture is an important source of variance of blood pressure particularly in ambulatory monitoring studies. Changing from the supine to the upright posture causes an increase of diastolic blood pressure with little or no change of systolic blood pressure. It has been shown that posture accounts for a major portion of overall variance of blood pressure in ambulatory monitoring studies [70]. However, this finding can largely be explained by taking into account the effects of the activities associated with different postures rather than the postures themselves. The changes of blood pressure occurring simply as the result of changing posture are rather modest. Coding for the average effect of

15 commonly occurring activities (including sleeping) on blood pressure (using the patient's clinic blood pressure as a covariate) can also account for much of the variance [71]. Time of day is a less important determinant of blood pressure.

Spontaneous short-term variability

Short term variability of blood pressure, of which respiratory fluctuation is the dominant cause, can be assessed only by beat-to-beat monitoring (e.g. using intra-arterial recording, or, recently, by using devices such as the Finapres and Portapres). Mancia *et al.* [72] studied variabilities of blood pressure and heart rate of a series of normotensive and hypertensive individuals using intra-arterial ABPM. Variability was expressed as the SD (i.e. the absolute level) and coefficient of variation (i.e. the percentage level), measured over two intervals, namely 30 min (short-term variability) and 24 h (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: during sleep there are decreases not only of blood pressure and heart rate, but also of their variabilities. With increasing age, there is an increase in short-term variability of blood pressure, but a decrease in variability of heart rate [72]. Spectral analysis has become very popular for analysing the short-term variabilities of blood pressure and heart rate, but it is not applicable to the intermittent recordings made with conventional non-invasive ABPM.

Comparison of variabilities of blood pressure in normotensive and hypertensive subjects

Authors of several studies using intra-arterial ABPM have shown that variability of blood pressure, usually measured as the SD of the daytime blood pressure, tends to be higher for hypertensives than it is for normotensives [73]. However, if variability is normalized by calculating the coefficient of variation, there is no longer any difference between normotensives and hypertensives [73]. Floras *et al.* [74] found that increasing variability of blood pressure was related not only to higher mean pressures but also to increasing age and diminishing baroreflex sensitivity.

How should variability of blood pressure be expressed?

An important consideration is the choice of an absolute as opposed to a relative measure of variability. The classic example of the former is the SD (in this case expressed in mmHg) and that of the latter is the coefficient of variation (the SD expressed as a percentage of the average level). Which is more appropriate has been the subject of considerable debate. In general, absolute measures of variability are preferred, because they keep variability and level of blood pressure distinct from each other. An important point

to stress is that outliers in the data will have a much greater effect on the variance or SD than they will on the mean, because they are derived from the square of the differences of individual readings from the mean. Furthermore, extreme positive and negative outliers will balance each other out in the estimation of the mean level, but will have the opposite effect for the estimation of variability. Since such outliers are quite likely to be artefactual readings, artefacts should ideally be eliminated from the data. The problem here is that we can never know which values are artefacts and which are true but extreme readings. A way out of this dilemma is to use non-parametric measures of variability, such as the interquartile range, which are less susceptible to the influence of outliers. This type of measure has been used relatively infrequently, but is valid and is particularly useful when there are outliers and artefacts.

Another measure is the root of the mean squared successive differences (RMSSD) [75]. The crucial difference from other measures of variability is that it takes into consideration the time sequence of the readings. The RMSSD is thus useful in situations in which short-term variability of blood pressure needs to be distinguished from a trend or step change in blood pressure. The cumulative-sum method might be useful for detecting a step change of blood pressure, such as occurs with the onsets of sleep and wakefulness [76].

Reproducibility

One of the problems with estimates of variability of blood pressure such as the SD obtained from ABPM is that they have a low test-re-test reliability [77]. This can be improved by standardizing activity on the two occasions. The RMSSD method also improves it [78].

References

- O'Brien E, Petrie J, Littler WA, de Swiet M, Padfield PL, Altman D, et al. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens* 1993; **11** (suppl 2):S43-S63.
- American national standard. *Electronic or automated sphygmomanometers*. Arlington, VA: Association for the Advancement of Medical Instrumentation; 1993.
- O'Brien E, Mee F, Atkins N, O'Malley K. The quest for better validation: a critical comparison of the AAMI and BHS validation protocols for ambulatory blood pressure measuring systems. *Biomed Instrumentation Technol* 1992; **26**:395-399.
- O'Brien E, Atkins N. 24-hour ABPM: technical aspects of 24 hour ambulatory blood pressure monitoring: comparative accuracy of six ambulatory systems determined by the BHS protocol. *High Blood Press* 1993; **2** (suppl 1):76-79.
- O'Brien E, O'Malley K, Atkins N, Mee F. A review of validation procedures for blood pressure measuring devices. In: Waeber B, O'Brien E, O'Malley K, Brunner HR (editors): *Twenty-four hour ambulatory blood pressure monitoring in clinical practice*. New York: Raven Press; 1994. pp. 1-32.
- O'Brien E. A review of standards for non-invasive blood pressure measurement. In: Pickering T (editor): *Ambulatory blood pressure*. Washington: SpaceLabs Medical; 1994. pp. 96-102.
- O'Brien E, Atkins N, Staessen J. Factors influencing validation of ambulatory blood pressure measuring devices. *J Hypertens* 1995; **13**:1235-1240.
- O'Shea JC, Murphy MB. Factors confounding assessment of ambulatory blood pressure monitors, studied during formal evaluation of the Tyco Quiet-Trak. *Am J Hypertens* 1997; **10**:175-180.
- O'Brien E, Atkins N. A comparison of the BHS and AAMI protocols for validating blood pressure measuring devices: can the two be reconciled? *J Hypertens* 1994; **12**:1089-1094.
- Formation of the working group on blood pressure monitoring of the European Society of Hypertension. *J Hypertens* 1998; **16**:893.
- Atkins N, O'Brien E. Towards a simpler and common protocol for the validation of blood pressure measuring devices. *Am J Hypertens* 1999; **12**:147A.
- Atkins N, O'Brien E, Wesseling KH, Guelen I. Increasing observer objectivity with audio-visual technology: the Sphygmocorder. *Blood Press Monit* 1997; **2**:269-272.
- The British Hypertension Society. *Blood Pressure Measurement* (CD-ROM). London: BMJ Books; 1998.
- Société Française d'Hypertension Artérielle. *La prise de la pression artérielle au cabinet médical*. Paris; 1998.
- Ng K-G. Considerations for simulation-based evaluation of noninvasive blood pressure monitors. *Blood Press Monit* 1997; **2**:257-268.
- De Gaudemaris. Software program for analysis of BHS validation data. 1999.
- O'Brien E, Mee F, Atkins N. Evaluation of the Schiller BR-102 ambulatory blood pressure system according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. *Blood Press Monit* 1999; **4**:35-43.
- Mallion JM, De Gaudemaris R, Baguet JP, Azzouzi L, Quesada JL, Sauzeau C, et al. Acceptability and tolerance of ambulatory blood pressure measurement in the hypertensive patient. *Blood Press Monit* 1996; **1**:197-203.
- Schneider RA, Costiloe JP. Twenty-four hour automatic monitoring of blood pressure and heart rate at work and at home. *Am Heart J* 1995; **90**:695-702.
- Di Rienzo M, Grassi G, Pedotti A, Mancia G. Continuous vs intermittent blood pressure measurements in estimating 24-hour average blood pressure. *Hypertension* 1983; **5**:264-269.
- Trazzi S, Mutti E, Frattola A, Imholz B, Parati G, Mancia G. Reproducibility of non-invasive and intra-arterial blood pressure monitoring: implications for studies on antihypertensive treatment. *J Hypertens* 1991; **9**:115-119.
- Palatini P, Mormino P, Canali C, Santonastaso M, De Venuto G, Zanata G, et al. Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST trial. *Hypertension* 1994; **23**:211-216.
- Palatini P, Mormino P, Santonastaso M, Mos L, Pessina A. Ambulatory blood pressure predicts end-organ damage only in subjects with reproducible recordings. *J Hypertens* 1999; **17**:465-473.
- Streitberg B, Mayer-Sabellek W, Baumgart P. Statistical analysis of circadian blood pressure recordings in controlled clinical trials. *J Hypertens* 1989; **7** (suppl 3):S11-S17.
- Thijs L, Staessen J, Fagard R, Zachariah P, Amery A. Number of measurements required for analysis of diurnal blood pressure profile. *J Hum Hypertens* 1994; **8**:239-244.
- Di Rienzo M, Parati G, Pomidossi G, Veniani M, Pedotti A, Mancia G. Blood pressure over short day and night times cannot predict 24-hour average blood pressure. *J Hypertens* 1985; **3**:343-349.
- Mancia G, Ulian L, Parati G, Trazzi S. Increase in blood pressure reproducibility by repeated semi-automatic blood pressure measurements in the clinic environment. *J Hypertens* 1994; **12**:469-473.
- Fotherby MD, Potter JF. Reproducibility of ambulatory and clinic blood pressure measurements in elderly hypertensive subjects. *J Hypertens* 1993; **11**:573-579.
- Sheps SG, Bailey KR, Zachariah PK. Short-term (six hour), ambulatory blood pressure monitoring. *J Hum Hypertens* 1994; **8**:873-878.
- Braun HJ, Rabouw H, Werner H, van Montfrans GA, De Stigter C, Zwiderman AH. Measurements of blood pressure with various techniques in daily practice: uncertainty in diagnosing office hypertension with short-term in-hospital registration of blood pressure. *Blood Press Monit* 1999; **4**:59-64.
- Coats AJS, Radaelli A, Clark SJ, Conway J, Sleight P. The influence of ambulatory blood pressure monitoring on the design and interpretation of trials in hypertension. *J Hypertens* 1992; **10**:385-391.
- Staessen JA, Thijs L, Mancia G, Parati G, O'Brien E. Clinical trials with ambulatory blood pressure monitoring: fewer patients needed? *Lancet* 1994; **344**:1552-1556.

- 33 Mancia G, Omboni S, Parati G, Trazzi S, Mutti E. Limited reproducibility of hourly blood pressure values obtained by ambulatory blood pressure monitoring: implications for studies on antihypertensive drugs. *J Hypertens* 1992; **10**:1531–1535.
- 34 Parati G, Bosi S, Castellano M, Cristofari M, Di Rienzo M, Germanò G, *et al.* Guidelines for 24h non-invasive ambulatory blood pressure monitoring. Report from a working group of the Italian Society of Hypertension. *High Blood Press* 1995; **4**:168–174.
- 35 Sayers BMCA, Ruggiero C, Feuerlicht J. Statistical variability of biomedical data: part 1. The influence of serial correlation on mean value estimates. *Med Inform* 1981; **6**:1–11.
- 36 Sayers BMCA, Ruggiero C, Feuerlicht J. Statistical variability of biomedical data: part 2. The influence of serial correlation on power estimates, and on comparative testing of samples. *Med Inform* 1981; **6**:207–220.
- 37 Sayers BMCA, Sandoval LS, Ruggiero C. Statistical sampling strategies for averaging purposes in serially correlated biomedical data. *Med Inform* 1981; **6**:271–278.
- 38 Oppenheim AV, Shafer RW. *Digital signal processing*. Englewood Cliffs, NJ: Prentice Hall, Inc. 1975.
- 39 O'Brien E. Automated blood pressure measurement: state of the market in 1998 and the need for an international validation protocol for blood pressure measuring devices. *Blood Press Monit* 1998; **3**:205–211.
- 40 Atkins N, O'Brien E. Computer analysis of blood pressure indices. *Blood Press Monit* 1996; **1** (suppl 1):S69–S72.
- 41 Atkins N, O'Brien E. DABL97—a computer program for the assessment of blood pressure, risk factors and cardiovascular target organ involvement in hypertension. *J Hypertens* 1998; **16** (suppl 2):S198.
- 42 Fagard R, Staessen J, Thijs L. Twenty-four hour blood pressure measurements: analytic aspects. *Blood Press Monit* 1996; **1** (suppl 1):S23–S25.
- 43 Fagard R, Staessen JA, Thijs L. The relationship between left ventricular mass and daytime and night-time blood pressures: a meta-analysis of comparative studies. *J Hypertens* 1995; **13**:823–829.
- 44 Peixoto Filho AJ, Mansoor GA, White WB. Effects of actual versus arbitrary awake and sleep times on analyses of 24-h blood pressure. *Am J Hypertens* 1995; **8**:676–680.
- 45 Halberg F. Chronobiology. *Ann Rev Physiol* 1969; **31**:675–725.
- 46 Thijs L, Staessen J, Fagard R. Analysis of the diurnal blood pressure profile. *High Blood Press* 1992; **1**:17–28.
- 47 Streitberg B, Meyer-Sabellek W, Baumgart P. Statistical analysis of circadian blood pressure recordings in clinical trials. *J Hypertens* 1989; **7** (suppl 3):S11–S17.
- 48 Hansen KW, Pedersen MM, Christiansen JS, Mogensen CE. Diurnal blood pressure variations in normo-albuminuric type I diabetic patients. *J Intern Med* 1993; **234**:175–180.
- 49 Gatzka CD, Schmieder RE. Improved classification of dippers by individualized analysis of ambulatory blood pressure profiles. *Am J Hypertens* 1995; **8**:666–671.
- 50 Rosansky SJ, Menackery SJ, Wagner CM, Jackson K. The effect of sleep intervals on analysis of 24-h ambulatory blood pressure data. *Am J Hypertens* 1995; **8**:672–675.
- 51 van Ittersum FJ, Yzerman RG, Stehouwer CDA, Donker AJM. Analysis of 24-hour ambulatory blood pressure monitoring: what time period to assess blood pressures during waking and sleeping. *J Hypertens* 1995; **13**:1053–1058.
- 52 Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24-h pressure analysis. *J Hypertens* 1996; **14**:557–563.
- 53 Gosse P, Ansoborlo P, Lemetayer P, Clementy J. Daytime and night-time ambulatory blood pressures should be calculated over the true sleep/waking cycle and not over arbitrary periods. *Am J Hypertens* 1996; **9**:269–272.
- 54 Stewart MJ, Brown H, Padfield PL. Can simultaneous ambulatory blood pressure and activity monitoring improve the definition of blood pressure? *Am J Hypertens* 1993; **6**:174S–178S.
- 55 Bursztyn M, Mekler J, Wachtel N, Ben-Ishay D. Siesta and ambulatory blood pressure monitoring. Comparability of the afternoon nap and night sleep. *Am J Hypertens* 1994; **7**:217–221.
- 56 Pelosio A, Longhi C, Marchetti P, Menniti-Ippolito F, Traversa G. Siesta, night sleep and blood pressure dropping. *Blood Press Monit* 1996; **2**:27–30.
- 57 Idema RN, Gelsema ES, Wenting G-J, Grashuis JL, van den Meiracker AH, Brouwer RML, *et al.* A new model for diurnal blood pressure profiling. Square wave fit compared with conventional methods. *Hypertension* 1992; **19**:595–605.
- 58 Thijs L, Celis H, Clement D, Gil-Extremera B, Kawecka-Jaszcz K, Mancia G, *et al.* Conventional and ambulatory blood pressure measurement in older patients with isolated systolic hypertension: second progress report on the ambulatory blood pressure monitoring project in the SYST-EUR trial. *Blood Press Monit* 1996; **1**:95–103.
- 59 Staessen JA, Bieniaszewski L, O'Brien E, Gosse P, Hayashi H, Imai Y, *et al.* Nocturnal blood pressure fall on ambulatory monitoring in a large international database. *Hypertension* 1997; **29**:30–39.
- 60 Stanton A, Cox J, Atkins N, O'Malley K, O'Brien E. Cumulative sums in quantifying circadian blood pressure patterns. *Hypertension* 1992; **19**:595–605.
- 61 The scientific committee. Consensus document on non-invasive ambulatory blood pressure monitoring. *J Hypertens* 1990; **8** (suppl 6):S135–S140.
- 62 Staessen J, Bulpitt CJ, Fagard R, Mancia G, O'Brien ET, Thijs L, *et al.* Reference values for the ambulatory blood pressure and the blood pressure measured at home: a population study. *J Hum Hypertens* 1991; **5**:355–361.
- 63 Staessen J, Thijs L, Bieniaszewski L, O'Brien E, Palatini P, Davidson C, *et al.* Ambulatory monitoring uncorrected for placebo overestimates long-term antihypertensive action. *Hypertension* 1996; **27**:414–420.
- 64 Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* 1997; **29**:22–29.
- 65 Fagard RH, Staessen JA, Thijs L. Relationships between changes in left ventricular mass and in clinic and ambulatory blood pressure in response to antihypertensive therapy. *J Hypertens* 1997; **15**:1493–1502.
- 66 Fagard RH, Staessen JA, Thijs L. Optimal definition of daytime and night-time blood pressure. *Blood Press Monit* 1997; **2**:315–321.
- 67 Mann S, Craig MW, Melville DI, Balasubramanian V, Raftery EB. Physical activity and the circadian rhythm of blood pressure. *Clin Sci* 1979; **57** (suppl 5):291s–294s.
- 68 Young MA, Rowlands DB, Stallard TJ, Watson RD, Littler WA. Effect of environment on blood pressure: home versus hospital. *BMJ* 1983; **286**:1235–1236.
- 69 van den Meiracker AH, Man in't Veld AJ, van Eck HJ, Wenting GJ, Schalekamp MA. Determinants of short-term blood pressure variability. Effects of bed rest and sensory deprivation in essential hypertension. *Am J Hypertens* 1988; **1**:22–26.
- 70 Gellman M, Spitzer S, Ironson G, Llabre M, Saab P, DeCarlo RP, *et al.* Posture, place and mood effects on ambulatory blood pressure. *Psychophysiology* 1990; **27**:544–551.
- 71 Clark LA, Denby L, Pregon D, Harshfield GA, Pickering TG, Blank S, *et al.* A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. *J Chron Dis* 1987; **40**:671–681.
- 72 Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, *et al.* Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983; **53**:96–104.
- 73 Watson RD, Stallard TJ, Flinn RM, Littler WA. Factors determining direct arterial pressure and its variability in hypertensive man. *Hypertension* 1980; **2**:333–341.
- 74 Floras JS, Hassan MO, Jones JV, Osikowska BA, Sever PS, Sleight P. Consequences of impaired arterial baroreflexes in essential hypertension: effects on pressor responses, plasma noradrenaline and blood pressure variability. *J Hypertens* 1988; **6**:525–535.
- 75 Schachinger H, Langewitz W, Schmieder RE, Ruddle H. Comparison of parameters for assessing blood pressure and heart rate variability from non-invasive twenty-four-hour blood pressure monitoring. *J Hypertens* 1989; **7** (suppl):S81–S84 [published erratum appears in *J Hypertens* 1989; **7** (suppl 9):767].
- 76 O'Brien E, Perry I, Sheridan J, Atkins N, O'Malley K. Application of cusums to ambulatory blood pressure data: a simple statistical technique for detecting trends over time. *J Hypertens* 1989; **7**:707–709.
- 77 James GD, Pickering TG, Yee LS, Harshfield GA, Riva S, Laragh JH. The reproducibility of average ambulatory, home, and clinic pressures. *Hypertension* 1988; **11**:545–549.
- 78 Gerin W, Rosofsky M, Pieper TG. A test of reproducibility of blood pressure and heart rate variability using a controlled ambulatory procedure. *J Hypertens* 1993 **11**:1127–1131.