PRACTICE REVIEW

The importance of 24-hour blood pressure in evaluating antihypertensive drug efficacy

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Summary

Conventional clinic measurement is influenced by many factors which make it an unsuitable technique for studies of antihypertensive drug efficacy. The major drawback of conventional measurement is that it cannot indicate the duration of drug effect, or the influence of antihypertensive drugs on nocturnal blood pressure. On the other hand, non-invasive 24-h ambulatory blood pressure measurement has a number of advantages: it provides a profile of blood pressure over the 24-h period, detects white coat responders and the design of studies of antihypertensive efficacy studies may be improved because the technique is devoid of the placebo response and provides so many more measurements. 24-h ambulatory blood pressure measurement also has an important role in the clinical management of hypertension in that it permits the prescribing doctor to select the antihypertensive drug most suited for the individual patient according to the 24-hour profile.

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.[1] Yet, despite the fact that these limitations are well documented, scientific papers on hypertension research often pay scant attention to the methodology of blood pressure measurement.[2] In fact, far-reaching decisions have often been made, both in relation to patient management and scientific research, without due consideration being given to the inherent deficiencies of the techniques available. The consequence of inaccuracy of blood pressure measurement is the misdiagnosis and overtreatment of blood pressure leading to substantial wastage of scarce resources and patients so diagnosed have had to endure the effects of being mislabelled as hypertensive and the unwanted effects of drug treatment. Similarly, inaccuracy of measurement must also lead to the erroneous classification of some hypertensive patients as normotensive with all the prognostic implications, though such an occurrence is less likely than overdiagnosing hypertension. Many of the inaccuracies of measurement arise from reliance on single or repeated conventional measurements often in artificial circumstances, such as a hospital clinic of general practitioner surgery, which may not bear much resemblance to blood pressure behaviour when the patient is carrying out normal activities at work or during recreation. The development of 24-hour ambulatory blood pressure measuring techniques over the past two decades has demonstrated clearly the deficiencies of conventional blood pressure measurement and the technique has now 'come of age' and has passed from the research arena to clinical practice.[3] It is timely, therefore, to review the short-comings of conventional blood pressure measurement and the advantages for patient management with 24-hour ambulatory techniques, particularly in the evaluation of antihypertensive drug medication.[4]

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Limitations of conventional blood pressure measurement

Traditionally blood pressure measurement in the evaluation of antihypertensive drug efficacy has been made by conventional sphygmomanometry using a mercury or research sphygmomanometer, such as the Hawksley random zero sphygmomanometer, and static semi-automated or automated devices. The limitations of conventional measurement in the assessment of antihypertensive drug efficacy have been reviewed elsewhere.[1] However, three points are worthy of brief reiteration:

Firstly, there is a most neglected source of error — the observer. In discussing observer competence we are faced immediately with three 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. 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.[1] Audiotape-training methods[2] have not generally met with success.[5] A number of films, the most recent of which has been produced by the British Hypertension

Society,[6] are available and are more successful in observer training than audio-tapes.[1]

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. Recommendations for the training and assessment of observers for the measurement of blood pressure in hypertension research are available.[5,7]

Blood pressure measurement by an observer using a standard mercury sphygmomanometer and stethoscope is subject to observer prejudice and terminal digit preference. The Hawksley random zero sphygmomanometer, which reduces observer bias but not digit preference, was designed to make research work more accurate. It has been accepted as the instrument of choice for epidemiological and research studies but recent studies have shown that the instrument systematically gives lower readings than the standard mercury sphygmomanometer[8] and the device can no longer be recommended.

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.[9]

Quite apart from the methodological problems already discussed, conventional measurement has a number of inherent features which include random variation, regression to the mean, the defence reaction and a placebo response, all of which render the assessment of antihypertensive drug efficacy difficult.

24-hour ambulatory blood pressure measurement in antihypertensive drug evaluation

Ambulatory blood pressure measurement over 24 hours has given new insights into blood pressure behaviour and is bringing about such a reappraisal of previously held concepts on hypertension that diagnostic and therapeutic decisions in practice are being critically evaluated.[11] In clinical research 24-hour ambulatory blood pressure measurement is providing exciting possibilities for the study of blood pressure behaviour, especially in the assessment of antihypertensive drug efficacy. Likewise, in clinical practice 24-hour blood pressure measurement facilitates drug prescribing in hypertension by providing evidence for the duration of drug effect thereby facilitating adjustment of drug dosage on an individual basis. 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; in improving the design of studies of antihypertensive drug efficacy; and its ability to demonstrate the effect of drugs on nocturnal blood pressure[11,12] and the potential problems associated with excessive lowering of blood pressure.[4]

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,[4,13] it is now more important than ever to be able to assess accurately 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.[4,13] 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 sphygmomanometer is vindicated, in that a fall in clinic blood pressure is confirmed by ambulatory measurement of daytime pressure.[13] 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.[13] 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[13] or are shown to be present only for a brief period coinciding with the observed clinic reduction.[4,13] Of considerable practical importance is the fact that many preparations which would have been declared as 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 to that operating in ambulatory circumstances.[13]

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 centred 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,[14] 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.

Detecting white coat responders
Anxiety raises blood pressure substantially. The defence or alarm reaction is a rise in blood pressure associated with blood pressure measurement.[15] This increase in blood pressure may subside once the subject becomes accustomed to the procedure 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'.[16] 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-recognised entity, can only be characterised 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.[16]

If patients with white coat hypertension are included in a study of antihypertensive drug efficacy, as is often the case when patients are recruited by the conventional clinic measurement, we might expect as many as one fifth of these patients not to have sustained hypertension[16] 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.[17]

Improved study design
An important difference between conventional and ambulatory blood pressure measurement is the absence of a placebo response with the latter, whether measurement is invasive or non-invasive.[4] 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.[4] A further advantage of ambulatory blood pressure measurement over conventional measurement in studies of antihypertensive drug efficacy is the reduction in the variability of blood pressure measurement thereby improving the precision with which blood pressure reduction can be quantified.[4,18]

24-hour ambulatory blood pressure measurement in selecting antihypertensive medication
Many of the principles enunciated above in relation to the advantages of 24-hour blood pressure measurement over conventional measurement apply also to prescribing antihypertensive drugs for the individual patient in clinical practice with the additional potential of ambulatory measurement to permit assessment of the effects of treatment on nocturnal pressure and perhaps to allow selection of the drug most appropriate for a particular circadian pattern of blood pressure.

Detection of antihypertensive drug effect and duration of action
Conventional measurement of blood pressure permits only assessment of the blood pressure lowering effect (or lack of it) at a particular moment in the 24-hour cycle. It may happen, for example, that the apparent lack of a blood pressure lowering effect with the conventional technique is merely a reflection of the relationship of the time of measurement to the time of administration of the drug and that if measurement was repeated an hour later a blood pressure lowering effect would be apparent. With 24-hour ambulatory measurement the prescribing physician is able to determine from the plot of pressure over time, the time of onset and the duration of effect of the prescribed antihypertensive drug.

Detecting white coat responders
Perhaps the greatest contribution of ambulatory blood pressure measurement to clinical practice is the ability of the technique to identify patients with white coat hypertension. In the United States, about 58 million people are hypertensive and about 35 million have blood pressures that would qualify them for treatment which, once started, will usually be for life. The estimated yearly cost of such treatment is $18-21 billion, including professional fees and laboratory tests. If we make the reasonable assumption that one quarter of these treated patients might have had white coat hypertension we are drawn to conclude that antihypertensive medication was prescribed to them unnecessarily. The estimated cost of such overprescribing has been estimated to be $5 billion each year.[19] In the seven years elapsing since this report was made, it may be anticipated that the estimated figure would now be appreciably more, especially with increasing use of expensive calcium channel blocking and angiotensin inhibiting drugs. In the light of such daunting figures the cost of 24-hour ambulatory measurement is readily justified. In a recent review of the cost-effectiveness of ambulatory blood pressure, Krakoff and his colleagues concluded that the technique would have a significant effect in reducing the costs of hypertension management.[20] It is, perhaps, worthy of mention that much is not known about white coat hypertension and that whereas patients with the condition may not need drug treatment at the time of diagnosis they certainly merit careful follow-up to determine if sustained hypertension develops later.

Nocturnal blood pressure, Load and Leese
There is now evidence that treated hypertensive patients whose blood pressures are lowest have the highest incidence of myocardial infarction.[21,22] For this reason, we must now direct our attention, not only to the efficacy of

blood pressure reduction but also to the magnitude of this reduction, the *leese* of pressure, (meaning literally the release or relaxation) as we have termed it.[4] This is especially relevant following the paper of Alderman and colleagues[22] showing that either a large or small reduction of blood pressure, especially diastolic pressure, is associated with a higher incidence of myocardial infarction, compared to those with an intermediate fall. 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[14] 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 significant reduction in nocturnal blood pressure (dippers).[11,12,23] Moreover, it has been recently demonstrated that end-organ damage, as judged by left ventricular size, is more severe in non-dippers than in dippers.[12] 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 might lead to myocardial ischaemia and infarction.[24] While the therapeutic and prognostic implications of these findings require further evaluation, they provide cogent evidence in favour of assessing the effects of antihypertensive therapy on sleeping blood pressure.

Effect of different drugs on circadian pattern

Consideration must be given to the possibility that the various groups of antihypertensive drugs may have differing effects on the circadian pattern of blood pressure or, put another way, the possibility that particular drugs may be more suited to patients with certain 24-hour patterns of blood pressure than others. We have shown in a retrospective analysis that hypertensive patients on beta-blockers have a significantly smaller nocturnal diastolic dip than hypertensives on no medication and this tendency was also present for systolic pressure. Hypertensives on ACE inhibitors have accentuated systolic and diastolic dipping patterns compared to patients on beta-blockers. Hypertensive patients treated with calcium antagonists or diuretics have similar diastolic and systolic dipping patterns to the untreated groups.[25]

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. In patients with an accentuated dip, for example, it may be advisable to use shorter acting drugs to be taken in the morning or to prescribe drugs which are known not to affect nocturnal pressure. On the other hand, hypertensive non-dippers require smooth blood pressure reduction throughout the 24-hour period, and it may be advantageous to attempt to restore a normal circadian pattern by using drugs known to be efficacious in reducing nocturnal pressure.

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 amassed over the past decade, is not now needed. Conventional clinic measurement is influenced by many factors which make the technique unsuitable for evaluating the efficacy of antihypertensive drug treatment over time. Though conventional measurement must remain the mainstay for monitoring blood pressure in clinical practice, it is necessary to assess 24-hour blood pressure when first making the diagnosis of hypertension, and at a later stage, when initiating or changing treatment especially in those patients who do not seem to respond to treatment.

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