Ambulatory blood pressure monitoring in the evaluation of drug efficacy

Conventional clinic measurement of blood pressure is influenced by many factors that make the technique unsuitable for the assessment 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. Noninvasive 24-hour ambulatory blood pressure measurement has a number of advantages over conventional measurement: it provides a profile of blood pressure over the 24-hour period; it detects white coat responders; it is free of regression to the mean and the placebo response, thereby making it possible to consider efficacy studies which need not have a placebo phase; it enables considerably more observations than is possible with clinic measurement by increasing the power of studies, which may reduce significantly the numbers of patients needed for antihypertensive drug studies. Twenty-four-hour ambulatory blood pressure measurement offers the opportunity to study antihypertensive drugs in fewer patients with greater accuracy than is possible with conventional clinic measurement and should be a mandatory requirement for such studies. (Am Heart J 1991;121:999-1006.)

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

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 (Hawksley and Sons Ltd., Lancing, Sussex, United Kingdom), and static semiautomated or automated devices. The limitations of conventional measurement in assessing antihypertensive drug efficacy, observer error, and device inaccuracy are major limitations of the conventional technique and have been reviewed elsewhere.[1]

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4/0/26249

Discussion of observer competence immediately raises three problems: identification of the potential sources of observer error; determination of what constitutes adequate training; and development of 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, audio tapes, and video films.[1] Audio tape training methods[2] have not generally met with success.[3] A number of films, the most recent of which has been produced by the British Hypertension Society,[4] are available and are more successful in observer training than audio tapes.[1]

In hypertension research not only is it desirable to train observers to a high level of accuracy, but also it is necessary to show that they have achieved this goal. An intensive observer training program 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 blood pressure measurement in hypertension research have been made.[3, 5]

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 epidemiologic and research studies, but a number of recent studies indicate that the instrument systematically gives lower readings than the standard mercury sphygmomanometer.[6-8] We have confirmed this and, thus, questioned its suitability for research and epidemiologic studies.[9]

One consequence of the increased interest in blood pressure measurement has been the creation of a large market for automated and semiautomated 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.[10] The availability of an automated device validated independently by present day criteria would be a distinct advantage in the evaluation of antihypertensive drug efficacy. Such a device would eliminate errors of interpretation, reduce or eliminate observer prejudice and terminal digit preference, obviate the necessity for elaborate observer training and assessment as described above, and, possibly, also reduce the white coat effect. No automated device has yet been shown conclusively to be as accurate as the mercury sphygmomanometer for the measurement of blood pressure. The advent of such a device is eagerly awaited.

Quite apart from the methodologic problems already discussed, conventional measurement has a number of inherent features that call into question its continuing role in antihypertensive drug studies. These include random variation, regression to the mean, the defense reaction, and the placebo response, all of which render the assessment of antihypertensive drug efficacy difficult. In fact, such are the limitations of conventional measurement that serious consideration must be given to its suitability for such studies. If, however, the technique continues to be used (as is likely), it must be accorded the care and attention to detail that is demanded of other scientific measurements.

24-HOUR AMBULATORY BLOOD PRESSURE MEASUREMENT

Ambulatory blood pressure measurement over 24 hours has given new insights into blood pressure behavior and is bringing about such a reappraisal of previously held concepts on hypertension that diagnostic and therapeutic decisions in practice are being critically evaluated.[11] Similarly, in clinical research, 24-hour ambulatory blood pressure measurement is providing exciting possibilities for the study of blood pressure behavior, especially in the assessment of antihypertensive drug efficacy. The advantages of 24-hour ambulatory measurement over conventional techniques may be considered in relation to the ability of the technique to detect drug effects that may not be evident with conventional measurement and in providing information on the duration of the antihypertensive effect. The technique can also improve the design of studies of antihypertensive drug efficacy, demonstrate the effect of drugs on nocturnal blood pressure, and detect excessive lowering of blood pressure by antihypertensive drugs.

The authors consider that the use of invasive intraarterial techniques for the measurement of ambulatory blood pressure in the evaluation of antihypertensive drugs is ethically acceptable only in exceptional circumstances and should be strictly confined to those few centers with a long experience and well-proven expertise in the technique; the discussion in this paper is, therefore, confined to noninvasive methods.

As with all innovative techniques, there comes the need for new terms to denote new phenomena. We have previously described hypertensive patients with a substantial nocturnal fall in blood pressure as "dippers" to distinguish them from those much fewer patients who do not show reduction in night-time pressure (the "nondippers").[12] These terms seem to have found acceptance.[13] Another descriptive term is now necessary after the work of White et al.[14] who demonstrated that blood pressure "load," as indicated by the percentage of systolic or diastolic measurements above normal during a 24-hour period, is a good predictor of left ventricular enlargement. By the same token, changes in the other direction, namely excessive reductions in blood pressure outside the lower limits of the normal range, need to be denoted. It is, therefore, proposed that the concept of load should indicate increases in blood pressure above the upper limits of normality and "leese" (meaning literally the release or relaxation) should denote a reduction in blood pressure below the lower limits. Before discussing such concepts, however, it is important to define the normal 24-hour blood pressure.

Normal 24-hour blood pressure. In conventional studies of antihypertensive drug efficacy, using the World Health Organization's (WHO) upper blood pressure limit for normotension simplified matters in that only the number of readings and the circumstances of measurement for entry into a study had to be decided. If ambulatory blood pressure levels are now to be used for entry criteria to drug studies, a

more daunting a task is faced at the very outset than was ever the case previously. The subsequent rewards, however, may be considerable.

Study of daytime and nighttime blood pressures in 776 men and women, aged 17 to 80 years, has shown that there are considerable differences between young and old, and that men have higher blood pressures than women during both daytime and nighttime;[15] to apply the levels of one to the other would be quite inappropriate. For example, to study the efficacy of a drug in both sexes (as is usually the case) and in subjects below the age of 65 years (as is commonly the case), without consideration of the differences in blood pressures between men and women and young and old would have serious implications in terms of simply deciding who was hypertensive and who was not. As a specific example, a study might have an entry criterion for mean daytime blood pressure of ≥140/85 mm Hg. A 20-year-old woman might be entered with a mean ambulatory daytime blood pressure of 142/90 mm Hg, which, in her case, is clearly hypertensive; with the upper limit of normality for her ambulatory daytime blood pressure being 133/87 mm Hg,[15] she comfortably fulfills the entry criterion. A 50-year-old man with the same mean daytime blood pressure would also fulfill the entry criterion, but would not be hypertensive for his age and sex, the upper limit of normality being 156/103 mm Hg.[15]

This aspect of patient selection for antihypertensive drug efficacy studies has been neglected in the face of scientific obduracy in being prepared to ignore the epidemiologic evidence that blood pressure, whether measured conventionally or with more elaborate techniques, varies with age and according to sex. The difficulties in overcoming this problem are not as great as they might at first appear. A number of population studies are attempting to determine the normal reference values for 24-hour blood pressure data and, with one large study already completed,[15] the reference levels for different groups will soon be evident. Furthermore, as evidence accumulates showing that 24-hour blood pressures are superior to conventional measurement in predicting end-organ effect,[13, 16, 17] the justification for study entry decisions being based on 24-hour rather than conventional measurement becomes stronger. If entry blood pressure could be based on, for example, daytime blood pressures according to age and sex, the recruitment of patients would be facilitated because it may become justifiable to enter patients with blood pressures that would be regarded as normotensive according to WHO criteria.

Detection of antihypertensive drug effect. One of the most surprising aspects of research into the efficacy of antihypertensive drugs is the readiness with which a blood pressure–lowering effect observed at one moment in the 24-hour cycle, often without reference to the time of drug administration, has been taken to indicate therapeutic efficacy throughout the day. With the increasing use of new formulations of drugs that permit once- or twice-daily dosage,[18] 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 study protocols of blood pressure–lowering drugs, and a number of patterns have emerged.[18] In some studies conventional clinic sphygmomanometry is vindicated in that a fall in clinic blood pressure is confirmed by ambulatory measurement of daytime blood pressure.[18] The ambulatory technique, however, 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 that is demonstrated by ambulatory measurement.[18] In these studies clinic blood pressure measurements may have been performed before the onset of a drug's antihypertensive effect. Finally, many studies have shown statistically significant reductions in clinic blood pressure which either are not confirmed by ambulatory measurement[18] or are shown to be present only for a brief period coinciding with the observed clinic reduction.[19, 20]

Of considerable practical importance is that preparations that could be declared as quite efficacious blood pressure–lowering agents by conventional measurement may be shown, by ambulatory measurement, to have a far less impressive pattern of activity. Some of the discrepancies between the two measurement 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, although there is evidence that the explanation is not always this simple. It is possible that the mechanism of reducing blood pressure in the clinic (and the amount of drug needed to do so) is different from that operating in ambulatory circumstances.[18]

Duration of antihypertensive drug effect. Ambulatory measurement provides what was only previously obtainable with direct invasive intraarterial measurement—an assessment of antihypertensive drug effect over 24 or 48 hours. Until recently, interest in this aspect of 24-hour measurement centered on the de-

sirability of being able to demonstrate that a drug was efficacious for the appropriate period related to dosing. This facility proved useful in demonstrating whether or not drugs possessed the duration of action claimed for them. The role of 24-hour blood pressure monitoring in detecting potentially dangerous excessive lowering of blood pressure with antihypertensive medication,[21] especially during the nocturnal period, may also prove to be very important.

Design of antihypertensive drug efficacy studies

White coat responders. Anxiety raises blood pressure substantially, and blood pressure measurement is associated with this defense or alarm reaction.[22] The increase in blood pressure may subside once the subject has become 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."[23] In this regard the alarm reaction to the process of blood pressure measurement may persist after several visits.

The white coat phenomenon, now a well-recognized entity, can best be characterized by ambulatory techniques of measurement. Pickering et al.[23] have shown that more than 20% of patients with borderline hypertension diagnosed by clinic measurement have normal daytime ambulatory blood pressure. A cautionary note, however, is necessary regarding the definition of hypertension because the WHO cut-off point for hypertension has tended to be widely applied to ambulatory measurement. For example, using a cut-off point of ≥160/95 mm Hg, 89% of patients referred to our blood pressure clinic would have been diagnosed hypertensive by the family practitioner using conventional measurement compared with 46% using noninvasive ambulatory measurement[24] because these comparisons were made before reference values for ambulatory measurement were available. Management decisions must now be made relative to the normal ambulatory levels of blood pressure and not to the long-serving WHO criteria, and this is especially so in judging the efficacy of antihypertensive drugs.

If patients with white coat hypertension are included in a study, as is often the case when patients are recruited by the conventional clinic measurement, as many as 20% of these patients might be expected not to have sustained hypertension[23] 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.[25]

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

Whatever terminology is used there is little doubt that the placebo phenomenon does exist[26] and has been demonstrated in most hypertensive patients,[27] although there have been some studies in which it has not been.[28] Placebo response may be an artifact of clinic blood pressure measurement associated with the inherent variability of arterial pressure, errors of measurement, regression to the mean, and increasing familiarity of the patient with the clinic procedure rather than being the result of the placebo itself.[28] Several clinic measurements are required to overcome these factors and ascertain the true level of blood pressure.[28] As a consequence, placebo control in studies dependent on isolated measurements is deemed mandatory,[27] although the inclusion of a placebo may lead to underestimation of antihypertensive drug efficacy.[28]

An important difference between conventional and ambulatory blood pressure measurement is the absence of a placebo response with the latter, whether measurement is invasive[28] or noninvasive,[29-32] although one study demonstrated a small but weakly statistically significant placebo response with daytime ambulatory measurement.[33] We have recently confirmed that the placebo response is not present with noninvasive 24-hour measurement (unpublished data, E.O.B.).

The absence of placebo effect with noninvasive ambulatory measurement may allow the opportunity of greatly simplifying the design and conduct of efficacy studies of antihypertensive drugs. Many investigators use a randomized, placebo-controlled crossover design on the basis that comparison between treatments in the same subject is more precise and requires fewer subjects than comparison between subjects. In such studies, a washout period before crossover is recommended to reduce the possibility of treatment-period interaction.[34] Lack of a placebo response, however, means that blood pressure measurements taken before and repeated after the treatment period are sufficient, making the crossover design, with its risk of carryover effects and the

need for prolonged placebo administration, unnecessary. This approach has been adopted by Raftery and his colleagues for the last decade using direct intraarterial ambulatory blood pressure measurement.[35]

Placebo may also be used in a run-in phase of antihypertensive drug evaluation to determine which patients remain, as it were, genuinely hypertensive. Many patients entering the placebo phase of a study on the basis of a diagnosis of mild to moderate hypertension by clinic blood pressure measurement fail to qualify for formal admission to the study because their blood pressures no longer meet the admission criteria. A placebo-controlled phase is included, therefore, in some studies to exclude subjects with normal blood pressure and to detect those who are truly hypertensive. A recent study by Gradman et al.,[36] however, showed that about 25% of patients designated hypertensive in this way had normal ambulatory blood pressures and that the use of a placebo-controlled run-in phase did not assure the selection of a genuine hypertensive population.

Regression to the mean. Regression to the mean potentially increases the number of responders in antihypertensive drug studies, especially in patients (such as the elderly) with the highest blood pressures. A placebo control group is, therefore, necessary to permit assessment of the number of true responders to the drug.[26] Ambulatory measurement, however, does not regress to the mean; hence subjects with high blood pressures do not exhibit a decrease in blood pressure and those with low blood pressures do not show a tendency to raise their pressure with repeated measurement.[37] This being so, ambulatory measurement may further enhance the likelihood of entering into a study only those patients with genuine hypertension.

Ambulatory measurement and sample size. It is becoming increasingly difficult to recruit patients for studies of antihypertensive drug efficacy. This may be attributed to a number of factors, some of which cannot be substantiated by factual documentation and are little more than impressions. Ethical restraints are, quite correctly, stricter and more perspicacious than in the past. Laudable as this may be, the reality is that efficacy studies are becoming more difficult to design, and this trend is likely to continue. There is also the impression that hypertension has now become a milder illness than before, and in many societies such as Ireland, where the standard of primary medical care is high, the number of patients coming to blood pressure clinics with severe hypertension is decreasing steadily, and accelerated hypertension has become a clinical rarity. What remains are patients who would previously have been designated as having mild hypertension, and the anticipated reduction in blood pressure with drugs in such patients has to be modest. With this realization also comes the problem of detecting a blood pressure–lowering effect in small numbers.[31, 38] To this must be added the reality of how difficult it is actually to find patients who fulfill the criteria for entry after the run-in or washout phases of a study. Recruiting patients who appear to be suitable may be relatively easy, but on entry, only 30% to 50% of those originally recruited may remain eligible. This rather skeptical but realistic view of patient recruitment contrasts with that of the Food and Drug Administration, which believes that, "Hypertension is widely prevalent, making study patients comparatively easy to find."[39]

Twenty-four-hour blood pressure measurements reduce the inherent variability associated with single blood pressure measurements, thereby improving the precision with which blood pressure reduction can be quantified.[31, 38] Coats et al.[38] have shown that the standard deviation of differences (S_D) for clinic measurements falls progressively from 12.6 to 6.5 mm Hg as the number of readings is increased from a single clinic reading to 20 ambulatory measurements. As the S_D falls so too does the number of subjects required for a study. Halving the S_D between readings approximately doubles the precision of the trial, thereby permitting a fourfold reduction in the number of subjects required to achieve an accurate result. For example, to detect a 5 mm Hg difference in diastolic blood pressure, halving the S_D, as might be possible with ambulatory measurement, would reduce the number of subjects needed in a parallel group trial from 250 to 67 and, for a crossover trial, from 61 to 16.[40]

This method has far-reaching implications for the design of antihypertensive studies and needs to be carefully evaluated in the light of increasing knowledge of ambulatory techniques. Applying this approach retrospectively to our studies of antihypertensive drug efficacy, a reduction in the S_D for systolic and diastolic blood pressures using ambulatory measurement was seen in only two cases, nicardipine[41] and ketansarin,[20] whereas in other studies the S_D increased for both systolic and diastolic blood pressures. In a study in which placebo rather than drug was given, the reduction in S_D for diastolic blood pressure was similar to that noted by Conway and Coats[40] who also used placebo, and it may be that the effect of antihypertensive drugs on the S_D is different from that of placebo. Other factors, such as the degree of activity during ambulatory recording, age, and lability of blood pressure, may also contribute to

the variable effect of drugs on the S_D. Whatever the explanation, this potentially important aspect of antihypertensive drug evaluation needs further study.

Nocturnal blood pressure: load and leese. There is now evidence that treated hypertensive patients in whom blood pressure reduction is greatest have the highest incidence of myocardial infarction.[42, 43] For this reason attention must be directed not only to the efficacy of blood pressure reduction in studies of antihypertensive drugs, but also to the magnitude of this reduction, the leese of pressure, as we have termed it. This is especially relevant after the paper of Alderman et al.,[43] which showed that both large and small reductions in blood pressure, especially diastolic blood pressure, appear to be associated with a higher incidence of myocardial infarction relative to a moderate fall. Reviewing the evidence that reducing blood pressure may increase the risk of myocardial infarction has led Berglund[21] to make the recommendation that, until further evidence is available, clinic diastolic blood pressure should not be reduced below 85 mm Hg, 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 (nondippers) are at greater risk than the majority who show a significant reduction in nocturnal blood pressure (dippers).[12, 13, 16] Moreover, it has recently been demonstrated that end-organ damage, as judged by left ventricular size, is more severe in nondippers than in dippers.[13, 16] The possibility also exists that antihypertensive drugs that have a prolonged duration of effect or are administered frequently may cause a profound reduction in nocturnal blood pressure in dippers, and that such hypotension might lead to myocardial ischemia and infarction.[44] Although the therapeutic and prognostic implications of these findings require further evaluation, they provide cogent evidence in favor of assessing the effects of antihypertensive therapy on blood pressure during sleep.

Effect of different drugs on circadian pattern. We have analyzed retrospectively 2859 records of 24-hour ambulatory blood pressure over a 3-year period to determine whether currently used antihypertensives had different effects on the circadian pattern.[45] Two important points emerged from this analysis. First, hypertensive patients receiving β-adrenoceptor blockers had a significantly smaller dip in nocturnal systolic blood pressure than patients receiving no medication. This tendency was also present for diastolic blood pressure, though it did not reach statistical significance. Second, hypertensive patients receiving angiotensin-converting enzyme (ACE) inhibitors had markedly accentuated patterns of dipping for their systolic and diastolic blood pressures compared with untreated patients and patients receiving β-blockers. Patients with hypertension treated with calcium antagonists or diuretics had similar dipping patterns to the untreated groups for systolic and diastolic blood pressures.

These small but significant differences in mean dips between the treatment groups result in quite marked alterations in the distribution of dipper-nondipper status. Nondipper frequency almost doubled among patients receiving β-blockers compared with those on no medication, and nearly three times as many patients on ACE inhibitors (21%) were dippers compared with untreated patients with hypertension (8%). 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. The only means of characterizing the magnitude of nocturnal dipping is by performing 24-hour blood pressure measurement. In patients with an accentuated dip, it may be advisable to use shorter-acting drugs to be taken in the morning or to prescribe drugs that are known not to affect nocturnal pressure. On the other hand, hypertensive nondippers 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 blood pressure.

CONCLUSIONS

The benefits of ambulatory blood pressure monitoring in assessing 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 are not now needed. Conventional clinic measurement is influenced by many factors that make the technique less than ideal for research into drug efficacy. More importantly, clinic measurement cannot provide a comprehensive assessment of duration of effect or the effect of antihypertensive drugs on blood pressure during sleep. Home measurement of blood pressure, although valuable in assessing blood pressure control in clinical practice, is not as infor-

mative as ambulatory blood pressure measurement and cannot provide measures of nocturnal blood pressures.

Owing to noninvasive ambulatory blood pressure monitoring being free of any placebo effect, it is now possible to consider efficacy studies that need not have a placebo phase, thus greatly simplifying the design of such studies. Moreover, the provision of considerably more observations than is possible with clinic measurement reduces within-subject variability and greatly increases the power of studies, thereby significantly reducing the numbers of patients needed for such studies.

Opponents to this line of reasoning will argue, with what should be diminishing conviction, that there are insufficient prognostic data to permit acceptance of the view that, on the one hand, inadequate reduction of 24-hour blood pressure by antihypertensive medication may be disadvantageous to patients or that, on the other hand, excessive reduction may possibly be more deleterious; and that decisions should be based on the time-honored and reliable prognostic data from conventional clinic blood pressure measurements. Whatever truth there is in this attitude, the circumstantial evidence deriving from end-organ studies (as distinct from long-term morbidity studies, which will take many years to perform at considerable cost) and the incidental benefits of the technique (such as the ability to diagnose the presence of persistent rather than transient or labile elevations in blood pressure and to evaluate the effects of antihypertensive medication over the 24-hour period) are so helpful in practice that the technique cannot but achieve wide popularity.

From the scientific viewpoint 24-hour blood pressure monitoring should lead to a fuller understanding of the mechanisms by which antihypertensive drugs lower blood pressure than was possible with conventional clinic measurement. The time has surely come when antihypertensive drug efficacy studies that do not assess blood pressure over 24 hours should no longer be acceptable.

Work cited in this paper has been supported by grants from the Charitable Infirmary Charitable Trust, the Health Research Board (Ireland), the Irish Heart Foundation and the Royal College of Surgeons in Ireland.

REFERENCES

1. O'Brien E, O'Malley K. Clinical blood pressure measurement. In: Robertson JIS, ed. Clinical hypertension. Handbook of hypertension, Vol 14. Amsterdam: Elsevier. (In press).
2. Roche V, O'Malley K, O'Brien E. How 'scientific' is blood pressure measurement in leading scientific journals? J Hypertens. (In press.)
3. O'Brien E, Tan KS, Atkins N, Mee F, O'Malley K. Training and assessment of observers for blood pressure measurement. J Hum Hypertens. (In press.)
4. Petrie J, Jamieson M, O'Brien E, et al. Blood pressure measurement videotape, prepared by the Working Party on Blood Pressure Measurement. London: British Medical Journal Publications, 1990.
5. O'Brien E, Petrie J, Littler WA, et al. British hypertension protocol: evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. J Hypertens 1990;8:607.
6. Evans JG, Prior IAM. Experience with the random-zero sphygmomanometer. Br J Prev Soc Med 1970;24:10.
7. De Gaudemaris R, Folsom AR, Prineas RJ, Luepker RV. The random-zero versus the standard mercury sphygmomanometer: a systematic blood pressure difference. Am J Epidemiol 1985;121:282.
8. Parker D, Liu K, Dyer AR, et al. A comparison of the random-zero and standard sphygmomanometers. Hypertension 1988; 11:269.
9. O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of the Hawksley random zero sphygmomanometer. Lancet. (In press.)
10. O'Brien E, Atkins N, Mee F, O'Malley K. Inaccuracy of seven popular sphygmomanometers for home-measurement of blood pressure. J Hypertens 1990;8:621.
11. O'Brien E, Fitzgerald D, O'Malley K. Blood pressure measurement: current practice and future trends. Br Med J 1985; 290:729.
12. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. Lancet 1988;2:397.
13. Pickering TG. The clinical significance of diurnal blood pressure variations: dippers and non-dippers. Circulation 1990; 81:700.
14. White WB, Dey HM, Schulman P. Assessment of the daily blood pressure load as a determinant of cardiac function in patients with mild to moderate hypertension. Am Heart J 1989;118:782.
15. O'Brien E, Murphy J, Tyndall A, et al. 24-Hour ambulatory blood pressure in normotensive subjects. Am J Hypertens 1990;3:35A.
16. Verdecchia P, Schillaci G, Guerreri M, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990;81:528.
17. Prisant LM, Carr AA, Wilson B, Converse S. Ambulatory blood pressure monitoring and echocardiographic left ventricular wall thickness and mass. Am J Hypertens 1990;3:81.
18. O'Brien E, Cox J, O'Malley K. Ambulatory blood pressure measurement in the evaluation of blood pressure lowering drugs. J Hypertens 1989;7:243.
19. Cox JP, O'Boyle CA, Mee F, et al. The antihypertensive efficacy of verapamil in the elderly evaluated by ambulatory blood pressure measurement. J Hum Hypertens 1988;2:41.
20. McCormack PME, Cox JP, Marron J, et al. The antihypertensive efficacy of ketansarin in the elderly evaluated by ambulatory blood pressure. J Hum Hypertens 1990;4:565-70.
21. Berglund G. Goals of antihypertensive therapy: is there a point beyond which reduction is dangerous? Am J Hypertens 1989;2:586.
22. Mancia G, Grassi G, Pomidossi G, et al. Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. Lancet 1983;2:695.
23. Pickering TG, James GD, Boddie C, et al. How common is white coat hypertension? JAMA 1988;259:225.
24. O'Brien E, O'Malley K. Overdiagnosing hypertension. Br Med J 1988;297:1211.
25. Waeber B, Scherrer U, Petrillo A, et al. Are some hypertensives overtreated? A prospective study of ambulatory blood pressure recording. Lancet 1987;2:732.
26. Bulpitt CJ. Responders and non-responders to antihypertensive treatment. Drugs 1988;35(suppl 6):142.
27. Doyle AE. Response to placebo treatment in hypertension. Hypertension 1983;5(suppl III):3.

28. Gould B, Mann S, Davies AB, et al. Does placebo lower blood-pressure? Lancet 1981;2:1377.
29. Drayer JIM, Weber MA, DeYoung JL, Brewer DD. Long-term BP monitoring in the evaluation of antihypertensive therapy. Arch Intern Med 1983;143:898.
30. Dupont AG, van der Niepen P, Six RO. Placebo does not lower ambulatory blood pressure. Br J Clin Pharmacol 1987;24:106.
31. Conway J, Johnston J, Coats A, et al. The use of ambulatory blood pressure monitoring to improve the accuracy and reduce the numbers of subjects in clinical trials of antihypertensive agents. J Hypertens 1988;6:111.
32. Cheung DG, Neutel JM, Smith DHG, et al. Absence of placebo effect on the whole-day ambulatory blood pressure (BP) (Abstract). Clin Pharmacol Ther 1990;47:200.
33. Bellet M, Pagny J-Y, Chatellier G, et al. Evaluation of slow release nicardipine in essential hypertension by casual and ambulatory blood pressure measurements. Effects of acute versus chronic administration. J Hypertens 1987;5:599.
34. Hills M, Armitage P. The two-period cross-over clinical trial. Br J Pharmacol 1979;8:7.
35. Mann S, Millar-Craig MW, Balasubramanian V. Propranolol LA and ambulatory blood pressure. Br J Clin Pharmacol 1980; 10:443-7.
36. Gradman AH, Pangan P, Germain M. Lack of correlation between clinic and 24-hour ambulatory blood pressure in subjects participating in a therapeutic drug trial. J Clin Epidemiol 1989;42:1049-54.
37. Fitzgerald DJ, O'Malley K, O'Brien ET. Reproducibility of ambulatory blood pressure recordings. In: Weber MA, Drayer JIM, eds. Ambulatory blood pressure monitoring. New York: Springer, 1984:71.
38. Coats A, Conway J, Sleight P. Ambulatory monitoring, clinical trial size and precision. J Hypertens 1989;7(suppl 6):S357.
39. Rose M, McMahon GF. Some problems with antihypertensive drug studies in the context of the new guidelines. Am J Hypertens 1990;3:151.
40. Cox JP, Ryan J, O'Brien E, O'Malley K. The effect of slow-release nicardipine on ambulatory and clinic blood pressure in mild hypertension. Br J Clin Pharmacol 1989;28:79.
41. Conway J, Coats A. Value of ambulatory blood pressure monitoring in clinical pharmacology. J Hypertens 1989;7(suppl 3):S29.
42. Cruickshank JM, Thorp JM, Sacharias FJ. Benefit and potential harm of lowering high blood pressure. Lancet 1987;1:581.
43. Alderman MH, Ooi WL, Madhavan S, Cohen H. Treatment-induced blood pressure reduction and the risk of myocardial infarction. JAMA 1989;262:920.
44. Floras JS. Antihypertensive treatment, myocardial infarction and nocturnal myocardial ischaemia. Lancet 1988;2:994.
45. Stanton AV, Atkins N, O'Malley K, O'Brien E. Circadian blood pressure and antihypertensive drugs. Am J Hypertens 1990;3:107A.