The Role of Ambulatory Blood Pressure Monitoring in Clinical Practice

Alberto Zanchetti

The introduction of noninvasive techniques for the repetitive measurement of blood pressure in ambulant subjects has permitted improved precision in the assessment of hypertension during normal daily life. The traditional clinic (or “office”) method of blood pressure measurement has the advantages of simplicity and low cost, and forms the basis of the current operational definitions of hypertension, but it is limited by the normal variability of blood pressure and the “white coat effect.” By contrast, ambulatory blood pressure provides information on circadian variations in blood pressure and alterations due to changes in behavior, and may, therefore, be more appropriate for diagnosing hypertension. However, it is important to note that the values used to define normotension and hypertension for clinic blood pressure are not appropriate for ambulatory blood pressure. Recent population studies have proposed that the upper limit for 24-h ambulatory pressure should be 119 to 126/75 to 80 mm Hg, and failure to recognize this may account for at least some cases of “white-coat hypertension.” There is increasing evidence that ambulatory blood pressure is more effective than clinic blood pressure in predicting the organ damage associated with hypertension, whereas data from intervention studies indicate that a reduction in ambulatory pressure is correlated with a reduction in left ventricular (LV) mass. Finally, ambulatory blood pressure measurements may provide a number of advantages in the development of antihypertensive therapies: by permitting better identification of trough and peak effects, by confirming that the efficacy of formulations for once-daily dosing is maintained throughout the 24-h period, and by minimizing the placebo effect.


KEY WORDS: Ambulatory blood pressure, hypertension, circadian variation, organ damage.

Blood pressure has been measurable in clinical practice since the meticulous work of Riva-Rocci 100 years ago.1,2 Consequently, arterial hypertension has been identified as a distinct clinical entity that can be assessed directly, rather than by indirect observations, such as the hardness of the pulse, the weight of the heart, or the presence of albuminous urine.3 In his brilliant and accurate papers on sphygmomanometry, Riva-Rocci remarked upon the variability of blood pressure values, and the influences that behavior and state of mind may exert on blood pressure.1–3 The introduction, in around 1969, of an intraarterial technique for beat-to-beat monitoring of blood pressure with a portable recorder4 provided a more faithful demonstration of the variability of blood pressure; not only from day to day, but also from moment to moment.5 It also showed how markedly blood pressure can be altered as a result of its measurement by a doctor or nurse (the “white-coat effect”).6 Indeed, it is somewhat paradox-
tional that a clinical condition such as arterial hyperten-
sion, which is defined in terms of blood pressure
values only, may be diagnosed on the basis of a few
occasional blood pressure measurements, and that
life-long treatment is often instituted following mea-
surements taken over just a few minutes.7,8

It is obvious that intraarterial blood pressure moni-
toring could not have a widespread application in
clinical practice. However, the introduction over the
last 10 years of noninvasive techniques for the repet-
itive sphygmomanometric measurement of blood
pressure with portable instruments has provided new
opportunities for the more precise assessment of blood
pressure.9 To compare the advantages of the two
methods for measuring blood pressure—the tradi-
tional measurement of blood pressure by a doctor or
nurse in the doctor’s office, outpatient clinic, or hos-
pital ward (usually called “clinic” or “office” blood
pressure) and the new techniques of 24-h blood pres-
sure monitoring in the ambulant subject (usually
called “ambulatory blood pressure”—the respective
values and limitations of these measurements will
briefly be discussed.

ADVANTAGES AND LIMITATIONS OF
CLINIC AND AMBULATORY BLOOD
PRESSURE MEASUREMENTS

Clinic Blood Pressure Clinic blood pressure mea-
measurement has two main advantages. The first is its
simplicity and, consequently, its low cost. The second
is that clinic blood pressure is the measurement that
has been used in all intervention trials by which the
benefits of antihypertensive therapy, and therefore the
current operational definition of hypertension, have
been established.8 Consequently, many experts main-
tain that clinic blood pressure is currently the only
valid measurement on which to base treatment deci-
sions.

The main limitations of clinic blood pressure mea-
surement are those already referred to: namely, the
marked variability of blood pressure measurements
and the white-coat effect. Throughout the many years
of clinical application of sphygmomanometry, various
methods have been designed in an attempt to improve
the reproducibility of clinic blood pressure measure-
ments. Even in his original papers, Riva-Rocci1,2 rec-
ommended that the conditions under which measure-
ments are made should be standardized. More re-
cently, specific recommendations have been provided
by various health organizations and scientific societies
(see, for example, those of the World Health Organi-
zation [WHO] and the International Society of Hyper-
tension [ISH]).10 Other methods have been designed
and suggested by several authors in order to better
standardize “resting” conditions during which mea-
surements should be performed, such as those sug-
gested by Smirk for taking basal blood pressure.11

In the Veterans Administration Cooperative Study
on Antihypertensive Agents,12 subjects were defined
as hypertensive when their blood pressures exceeded
recruitment threshold values following a few days in
hospital to habituate them to the blood pressure mea-
suring procedures. This approach, however, has not
been followed in any of the other randomized trials of
antihypertensive therapy. In these trials, investigators
were content to recruit patients after few visits and
measurements and, as a result, most of these trials
found that blood pressure had fallen considerably af-
 ter 3 to 6 months, even in patients randomized to
receive placebo. As a consequence, expert committee
guidelines10 recommend that, in patients with mild
hypertension, the diagnosis of hypertension and deci-
sions on treatment should be deferred for 3 to 6
months, during which time the existence of sustained
hypertension should be established. In spite of these
useful precautions, the correlation between clinic
blood pressure values and hypertension-related organ
damage remains relatively poor.9,13

Ambulatory Blood Pressure Ambulatory blood pre-
sure monitoring is undoubtedly attractive as it provides
many measurements over an extended period of time
(70 to 100 measurements in 24 h), gives information on
circadian variations in blood pressure, and documents
blood pressure responses to different behaviors. How-
ever, a series of problems associated with this method
should be given due consideration, including reliability
of the machines, establishment of “normal” values for
ambulatory blood pressure, and the use of ambulatory
blood pressure as a predictor of hypertension outcomes.
The first of these problems will be discussed briefly now,
whereas the other two problems will be considered in
subsequent sections of this review.

Reliability of the techniques used to measure blood
pressure is, obviously, a basic issue, and Riva-Rocci1,2
insisted on the superiority of the mercury manometer
over other devices. Validation of ambulatory blood
pressure measuring devices is therefore necessary.
Two validation protocols have been developed, one by
the British Hypertension Society14 and the other by the
Association for the Advancement of Medical Instru-
mentation.15 Despite the existence of these protocols,
O’Brien et al in a recent review16 remarked that, of the
43 ambulatory blood pressure monitoring devices cur-
rently marketed, only 18 have been validated accord-
ing to either of the two protocols. However, with the
proviso that the subject should rest with the arm kept
still while each measurement is taken, it can be con-
cluded that a number of satisfactorily accurate devices
for ambulatory blood pressure monitoring do exist.
Individual instruments should be checked before use,
and the data obtained should be edited according to preestablished criteria and programs to optimize reliability of data collection.

**AMBULATORY BLOOD PRESSURE MONITORING AS A DIAGNOSTIC TOOL**

**Normality Values** The potential use of ambulatory blood pressure monitoring for the diagnosis of hypertension has been limited by the lack of suitable data to define the values of ambulatory systolic and diastolic blood pressure that separate normotension from hypertension. For clinic blood pressure, the arbitrary dividing line has been set at 140/90 mm Hg, as these are the values above which intervention trials have shown significant benefits of blood pressure reduction. However, it is not logical to use the same values as a dividing line for treatment following ambulatory blood pressure measurement. Any type of measurement has its own normality values, and thus normality limits calculated for clinic blood pressure cannot also be used as normality limits for ambulatory blood pressure. Due to the lack of data from prospective intervention trials based on ambulatory blood pressure monitoring, normality values for ambulatory blood pressure have been calculated from larger or smaller cohorts of subjects defined as normotensive on the basis of previous clinic blood pressure measurements. This approach has been subjected to some criticism as the samples selected were not representative of the population as a whole, while normality, by definition, can only be described by population studies.

Three population studies have recently been performed in an attempt to define normal values for blood pressure obtained by ambulatory monitoring. The largest of these, the Studi delle Pressioni Ambulatoriali delle Laro Associazioni (PAMELA), was carried out in a randomized sample of the population of the Italian city of Monza (1651 subjects of the 2400 randomized). According to this study, both home and ambulatory blood pressure values, averaged either over 24 h or over daytime hours only, are several millimeters of mercury lower than values measured in the clinic. The differences between the values for clinic and 24-h average ambulatory blood pressure increased with increasing age (Figure 1), and also with increasing clinic blood pressure values (Figure 2). The upper limit of normal blood pressure values can be calculated as the values that correspond in a regression equation to 140/90 mm Hg clinic blood pressure: these values are 119 to 126/75 to 80 mm Hg for 24-h ambulatory blood pressure and 125 to 132/80 to 85 mm Hg for daytime ambulatory blood pressure. It has been proposed, therefore, that they can be used as an approximate dividing line between normotension and hypertension for ambulatory blood pressure.

**Isolated Clinic Hypertension (“White-Coat Hypertension”)** While interest in ambulatory blood pressure monitoring has been mounting, the term “white-coat hypertension” has gained acceptance and is often used to define a new clinical entity, namely, those subjects whose clinic blood pressure is in the hypertensive range, but whose ambulatory blood pressure is in the normotensive range. The term “white-coat” has been given to this type of hypertension on the assumption that the differences between clinic and ambulatory blood pressures are due to the white-coat effect; that is, the rise in blood pressure that often occurs when blood pressure is measured by a doctor or nurse.

The wide interest in white-coat hypertension is appropriate, as identification of individuals in whom blood pressure is raised only temporarily as an emotional reaction to the clinical environment may prevent unnecessary treatment of people whose blood pressure is normal during routine daily life. However, the significance of white-coat hypertension is still beleaguered by a series of problems that have produced misconceptions, misnomers, and misunderstandings. The first problem, defining the upper limit of normality for ambulatory blood pressure, has
already been discussed. The very high prevalence of white-coat hypertension that has been claimed by some authors derives from the misuse of 140/90 mm Hg as the upper limit of normality for both clinic and ambulatory blood pressure. By contrast, if 130/85 mm Hg is taken as the upper limit of normality for daytime ambulatory blood pressure, as suggested by PAMELA and other population studies, then the prevalence of white-coat hypertension is considerably lower. According to the PAMELA data, these individuals represent 10% to 15% of the hypertensive population, clearly a minority, but still a consistent proportion of hypertensive subjects.

A second problem is that there is no clear demonstration that the differences between clinic and ambulatory blood pressures are actually due to the white-coat effect. Although this probably does play a role, other factors are equally likely to account for the difference; for example, regression to the mean due to multiple measurements. The term white-coat hypertension may, therefore, be a misnomer and the new WHO report on hypertension control discourages the use of this term and suggests the more descriptive term “isolated clinic hypertension.”

The final problem is that of the possible risks associated with isolated clinic hypertension. Indeed, there is also considerable misunderstanding surrounding this crucial issue, and the available data could hardly be more contradictory. Some studies have reported that white-coat hypertension is associated with organ damage and metabolic disturbances, while others have denied the existence of any such association. Furthermore, although one follow-up study found that patients with white-coat hypertension had a cardiovascular morbidity similar to that of normotensive subjects, another study showed that a large proportion of such patients had a rapid increase in ambulatory blood pressure to abnormal values.

Nighttime Blood Pressure: “Dippers” versus “Nondippers” The possibility of noninvasive measurement of blood pressure at night and during sleep by ambulatory monitoring devices has stimulated interest in the pathophysiological significance of nighttime blood pressure. Two opposite concerns have been expressed: first, the risk of excessively low blood pressure values at night (especially as an effect of treatment), and second, the risk of a less than physiological fall in blood pressure during night sleep. The first type of risk, formulated in the context of the substantially unproved J-curve hypothesis, does not appear to be a serious one. Even during night sleep, blood pressure in patients with hypertension remains higher than in normotensive subjects. Furthermore, during bed sleep, perfusion of the brain is facilitated by the supine posture while cardiac perfusion is facilitated by simultaneous bradycardia.

The second type of risk has been given more attention, and it has become usual to subdivide hypertensive patients into “dippers” and “nondippers,” according to whether they have a greater or smaller fall in nighttime blood pressure. According to this subdivision, “nondipper” hypertensives would have a greater risk of left ventricular (LV) hypertrophy and of cardiovascular events than “dippers.” However, there are a number of problems with this subdivision. First, it has been remarked that different definitions of daytime and nighttime periods have been given in different papers, thus making calculations of the dipping phenomenon variable. Furthermore, in a population such as that investigated in the PAMELA study, the magnitude of nighttime changes in blood pressure has a normal-like distribution, and therefore the procedure of separating individuals into “dippers” and “nondippers” on the basis of a 10% reduction in nocturnal blood pressure is arbitrary. Finally, the differences between daytime and nighttime blood pressures are scarcely reproducible in the same subjects, as nighttime blood pressure is markedly influenced by the quality of sleep, and this is not commonly monitored in ambulatory blood pressure studies.
Secondary Hypertension  Ambulatory blood pressure monitoring has been recommended in the diagnosis of secondary forms of hypertension, as it is believed that these are not associated with circadian variations in blood pressure.\cite{37,48} Recent data, however, have shown that at least some patients with secondary hypertension have normal day and night fluctuations in arterial pressure.\cite{49–52}

Orthostatic Hypotension  Ambulatory blood pressure monitoring is useful in describing the 24-h blood pressure profile of patients with orthostatic hypotension, which is commonly characterized by a nocturnal rise, rather than a fall, in blood pressure during the time the patients spend in bed. Falls in blood pressure during exercise and after meals can also be measured more precisely with ambulatory monitoring.

**AMBULATORY BLOOD PRESSURE AS PREDICTOR OF ORGAN DAMAGE AND EVENTS**

**Blood Pressure Level**  The notion that hypertension is associated with increased cardiovascular morbidity and mortality is based largely on clinic blood pressure measurements, but, as has been remarked above, the predictive power of those measurements is weak, especially in mild and moderate hypertension. There is only one prospective study, by Perloff et al,\cite{54} that has suggested the superiority of repeated semiautomated ambulatory measurements during the day as a predictor of cardiovascular complications. However, because of its design, this study does not provide quantitative indications that may be useful in clinical practice. A recent study by Verdecchia et al\cite{39} shows that, among patients with clinic blood pressure in the hypertensive range, those with ambulatory blood pressure that is also in the hypertensive range have a significantly greater incidence of cardiovascular events than subjects with ambulatory blood pressure in the normotensive range. Unfortunately, it lacks the statistical power to demonstrate a clear predictive superiority of ambulatory over clinic blood pressure measurement. Nonetheless, a wealth of cross-sectional studies indicate that 24-h average blood pressure is correlated to a much greater extent than clinic blood pressure with hypertension-related organ damage, such as LV hypertrophy, microalbuminuria, and cerebral ischemia.\cite{57} In a more general study involving 106 patients with hypertension, Parati et al\cite{38} found that, although organ damage increased progressively from groups with lower to groups with higher clinic blood pressure, both the prevalence and the severity of organ damage within each group was clearly greater in subgroups of patients with a higher mean 24-h blood pressure.

Although there is a general consensus on the closer correlation of organ damage, particularly LV hypertrophy, with ambulatory than with clinic blood pressure, the relative importance of daytime and nighttime blood pressure and of day–night differences in blood pressure (“dipping”) has been the subject of contrasting reports. Recently, Fagard et al\cite{50} have performed a metaanalysis of 19 comparative studies, involving 1223 participants, and have concluded that nighttime blood pressure is not a significantly better predictor of LV mass than daytime blood pressure. In addition, the relationship between the day–night blood pressure difference and organ damage is not a unanimous finding and is only weakly significant. A report that LV hypertrophy is closely correlated with blood pressure while at work should also be mentioned.\cite{50}

The limitations inherent in the cross-sectional nature of all studies associating ambulatory blood pressure and signs of organ damage should not be forgotten. Prospective trials to compare the respective values of clinic and ambulatory blood pressures are often advocated, even in official guidelines, but these trials would be extremely difficult to conduct.\cite{61} It is likely that more practical information will be derived from intervention trials in which treatment outcomes are correlated with changes both in clinic and in ambulatory blood pressure.\cite{65,66} The first of these studies, the Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation (SAMPLE),\cite{67} has recently been completed. In this study, 206 patients with hypertension who also had marked LV hypertrophy were given the angiotensin converting enzyme (ACE) inhibitor lisinopril, 20 mg once daily, which was eventually supplemented with hydrochlorothiazide, for 12 months. Lisinopril treatment markedly reduced the LV mass index from 157.5 ± 32.0 g/m² to 133.4 ± 25.8 g/m² as assessed by echocardiography. Before treatment, LV mass index did not correlate with either clinic or home blood pressure, whereas it showed a significant correlation with 24-h average systolic and diastolic blood pressures (r = 0.34 and 0.27, respectively, P < .001). Furthermore, the reduction in LV mass was not related to the reduction in clinic or home blood pressure, but it was significantly related to the reduction in 24-h average systolic and diastolic blood pressure (r = 0.42 and 0.38, respectively, P < .001). In addition, it was found that the average daytime blood pressure accounted for this correlation, with little contribution of nighttime blood pressure or day–night blood pressure differences. Thus, regression of LV hypertrophy, such as that induced by lisinopril, can be predicted by treatment-induced changes in 24-h ambulatory blood pressure, but not by reductions in either clinic or home blood pressures. This clearly supports the possibility that, prognostically, ambulatory blood pressure is superior to clinic blood pressure.

Another recent study with nisoldipine coat-core (ni-
soldipine CC), the sustained release formulation of the dihydropyridine calcium channel blocker (CCB) nisoldipine, in black patients with severe hypertension found that, following 4 months of treatment, significant reductions in systolic and diastolic pressures were achieved ($P < .001$), which were shown by ambulatory monitoring to be maintained over 24 h. As with lisinopril, echocardiography showed that LV mass index was reduced by nisoldipine treatment, from 148 ± 41 g/m² at baseline to 127 ± 34 g/m² at 4 months ($P = .01$). Skoularigis et al have reported comparable results with amlodipine in a similar population. Other ongoing trials, either having cardiovascular events or organ damage measurements as endpoints, are also planned to explore the correlation between endpoints and clinic and ambulatory blood pressure values.

**Blood Pressure Variability** There is both a physiological and a clinical interest in being able to assess blood pressure variability during a 24-h period. Mancia et al have remarked that correct indices of variability can only be obtained by beat-to-beat blood pressure monitoring; for example, 24-h intraarterial recording provides indices of so-called long-term variability (24-h standard deviation) and short-term variability (half-hour standard deviation). Obviously, blood pressure monitoring by the usual noninvasive, intermittent devices provides less reliable indices of variability, depending on the frequency with which blood pressure is recorded.

The clinical interest in assessing blood pressure variability is strengthened by two cross-sectional studies that have shown that increased blood pressure variability can indeed be correlated with organ damage in patients with hypertension. Parati et al have reported that, among groups of hypertensive patients with the same 24-h average blood pressure, those with higher indices of variability (higher 24-h standard deviations) also had a greater prevalence and severity of organ damage. The relevance of these data is strengthened by the results of the follow-up of these patients, which showed that blood pressure variability at the time of the first study was significantly correlated with the progression of organ damage in subsequent years (Figure 3). This study provides the first prospective evidence for the prognostic importance of blood pressure variability.

The mechanisms of blood pressure variability are still incompletely understood. A considerable proportion of this variability is due to behavioral influences, presumably through central modulation of autonomic drive to the heart and blood vessels, upon which the baroreflexes exert a buffering influence. In addition, computer analysis of beat-to-beat arterial pressure tracings has recently indicated that part of the variability in blood pressure is due to rhythmic slow oscillations of different frequencies, which can be identified and quantified by power spectral analysis. The implications of these important studies, however, are beyond the scope of the present review.

**Blood Pressure Load** The product of the time and the extent by which blood pressure remains higher than the upper level of normotension has been defined as “blood pressure load,” and this factor has been proposed as a more precise measure of blood pressure risk than the level of hypertension alone. Unfortunately, the blood pressure load has often been calculated using 140/90 mm Hg as the upper limit for normotension and, as has been mentioned previously in this review, the upper limit of normotension for ambulatory blood pressure is lower than this. In addition, a correct calculation of “load” should be referred to different blood pressure levels for daytime and nighttime. Finally, there is no clear evidence that calculation of the blood pressure load adds any significant precision to the calculation of 24-h, daytime, or nighttime averages, or variability.

**AMBULATORY BLOOD PRESSURE MONITORING IN THE ASSESSMENT OF ANTIHYPERTENSIVE THERAPY**

“Smooth” or uniform blood pressure control is an obvious goal of antihypertensive therapy, but it is
difficult to measure by the traditional clinic blood pressure measurements. Ambulatory blood pressure monitoring, therefore, is used increasingly to evaluate new antihypertensive drugs and to assess the adequacy of treatment. This application is based on the assumption that treatment must be continuously adequate and that more frequent blood pressure measurements during treatment, particularly at different times and during various types of activity or mental states, may lead to a more accurate assessment than infrequent measurements in the clinic.

The Trough:Peak Ratio Because most of the clinical studies used for regulatory purposes are based on clinic blood pressure measurement, the US Food and Drug Administration (FDA) has suggested a simplified arithmetic standard, called the trough:peak ratio, to obtain an approximate, but simple, index of smoothness of the antihypertensive action of a drug. The trough:peak ratio is the ratio between the effect of an antihypertensive agent at the end of the interval between doses (for a drug administered once daily, the ‘trough’ is 24-h postdose) and at the time of its maximum effect (the peak blood pressure effect is arbitrarily measured at the time of the peak pharmacokinetic effect).

When the effect of an antihypertensive agent is assessed by clinic blood pressure, it is found that placebo administration is also accompanied by a significant decrease in blood pressure. Therefore a correct calculation of the trough:peak ratio requires that the effects observed in a parallel, placebo-treated group are subtracted from the trough:peak values measured in the actively treated group. FDA guidelines require that placebo-corrected trough:peak ratios should be at least 0.5, and more than 0.65 if the peak effect does not produce a reduction in blood pressure > 5 mm Hg. Obviously, the closer the ratio is to one, the more likely the drug will be to produce a uniform antihypertensive response.

Ambulatory blood pressure monitoring, by recording blood pressure every 15 to 30 min, is expected to allow better recognition of peak and trough effects. In addition, measurement under real-life conditions, as in ambulatory monitoring, offers a potential advantage, although it may also have some disadvantages. In fact, changes at both peak and trough are calculated by subtracting blood pressure values obtained during the treatment day from values obtained at the same time of the day during the placebo run-in day, and even slight differences in behavior during the 2 days may cause some inaccuracy in estimation. In a recent analysis of several therapeutic studies pooled together, Omboni et al found that the best compromise between a correct estimate of peak changes and reproducibility was the average of the adjacent 2 h with the maximum blood pressure fall; they also advise the use of the average of the last 2 h as an estimate of trough. When ambulatory blood pressure monitoring is used, very little or no placebo effect is observed. Therefore, in parallel-group studies, placebo correction may introduce a source of error because of the potentially different behaviors in the placebo and active-treatment groups. However, placebo correction may be performed for each subject in cross-over studies.

Trough:peak ratios have traditionally been expressed as group ratios; that is, as the ratios of the mean trough and the mean peak values in the group of treated patients. The clinical goal of treatment, however, is that the antihypertensive effect should not vary greatly during the day in individual patients. However, calculation of individual ratios and of the percentage of patients with a suitably high ratio, although of undoubted clinical interest, is fraught with problems, mostly because nonresponder patients may have quite erratic ratios. Calculation of individual ratios limited to responders gives reliable information, but with obvious statistical limitations, because the analysis is restricted to only a proportion of all randomized patients. These individual ratios, however, are clinically helpful and may provide supportive and descriptive evidence.

The Goal of Treatment: 24-h, Daytime, Nighttime, or Hourly Blood Pressure Values? Beyond the usefulness of a more precise calculation of the trough:peak ratio, only ambulatory blood pressure monitoring can accurately verify whether antihypertensive therapy can really provide a uniform 24-h blood pressure control: that is, a uniform reduction of blood pressure throughout the 24-h period. As has been mentioned above, blood pressure values both in normotensive and hypertensive subjects are known to differ markedly between daytime and nighttime, with nighttime values considerably lower. One question which has been raised is whether it is 24-h, daytime, or nighttime average blood pressure that should be more effectively normalized by antihypertensive therapy. Divergent opinions exist on this issue, originating from the contrasting data on the correlation of organ damage, particularly LV hypertrophy, with daytime versus nighttime blood pressure. It has been mentioned already that a recent metaanalysis has shown that both daytime and nighttime average blood pressures are equally well correlated with LV mass index. Therefore, in the absence of crucial prospective evidence on the predictive capacity of any ambulatory blood pressure measurement, a reduction in both daytime and nighttime blood pressure appears the most reasonable goal of antihypertensive therapy.

If detailed information on the achievement and maintenance under therapy of a normal blood pres-
pressure pattern is required, then the so-called hourly blood pressure profiles (ie, the sequence of hourly means of systolic and diastolic blood pressure during the entire 24-h period) provide the most extensive information. In drug studies, the blood pressure profile during a placebo run-in period can be compared with the blood pressure profile at predetermined times (weeks or months) after the beginning of active treatment. For clinical purposes, individual 24-h blood pressure profiles before treatment or under previous treatment can be compared with profiles obtained during treatment or treatment adjustment. However, the limited reproducibility of hourly blood pressure values, especially when ambulatory monitoring is repeated at intervals of several weeks, may cause some difficulties, especially for individual assessments of therapy.

Additional caution should be used when taking advantage of ambulatory monitoring in the evaluation of therapy. As clearly indicated in the WHO/ISH guidelines for the management of hypertension, "When home blood pressure or ambulatory blood pressure measurements are used to help in the evaluation of blood pressure achieved by treatment, it should be remembered that blood pressure values provided by these methods are on the average several mm Hg lower than clinic blood pressures; therefore, treatment-goal blood pressure when assessed by these techniques should be set at a lower level to avoid undertreatment." However, after several weeks of antihypertensive treatment, the difference between clinic and ambulatory blood pressure values is significantly attenuated. Therefore, when measured by ambulatory blood pressure, the effect of antihypertensive treatment is considerably attenuated.

Clinical Studies Using Ambulatory Blood Pressure

In recent years a major goal in the development of antihypertensive therapy has been to develop drugs that permit once-daily dosing. It is important, however, to show that such agents really do provide effective control of blood pressure throughout the 24-h period, and the clinical development of all new antihypertensive drugs now includes some trials that use ambulatory blood pressure monitoring.

The results of the SAMPLE study, which showed that the 24-h efficacy of lisinopril is correlated with a reduction in LV mass, have already been discussed. Another study demonstrated that lisinopril was significantly more effective than hydralazine at lowering nighttime blood pressure, and suggested that this accounted for the reduction in LV hypertrophy in the lisinopril-treated patients, whereas no effect was seen on LV mass in the patients who received hydralazine. However, as previously mentioned, the SAMPLE study suggests that the reduction in nighttime blood pressure values contributes only to a rather limited extent to the reduction in LV mass induced by lisinopril. Recently, Guthrie et al have demonstrated significant reductions in systolic and diastolic pressures over the 24-h period with a fosinopril/hydrochlorothiazide combination, whereas ambulatory monitoring showed that there was no response with placebo. Furthermore, this study indicated that ambulatory blood pressure was more sensitive than clinic blood pressure at identifying possible differences in response with different doses of the fosinopril/hydrochlorothiazide combination. Ambulatory blood pressure has also demonstrated the efficacy of a once-daily dose of the angiotensin II receptor antagonist losartan. As in other studies, ambulatory blood pressure measurement virtually abolished the placebo response in this study.

Several studies using ambulatory blood pressure monitoring have been performed with long-acting dihydropyridine CCB. These studies have demonstrated that 5 mg amlodipine daily, 10 mg extended-release felodipine daily, and 30 mg nifedipine gastrointestinal therapeutic system (nifedipine GITS) daily all produce significant reductions in blood pressure, and that this effect is maintained for at least 24 h. Such studies have also shown that the antihypertensive effects of some of these agents may be maintained for more than 24 h. For example, nifedipine GITS has been shown to reduce blood pressure for up to 36 h, while a single dose of amlodipine lowers blood pressure for 48 h.

Recent studies of ambulatory blood pressure have also been performed with nisoldipine CC, which has a trough:peak ratio close to 1.8 These studies have shown that 10, 20, and 30 mg nisoldipine CC daily reduces blood pressure throughout the 24-h period, without altering the normal circadian variation, and that it has a smooth onset of effect, as might be predicted from the trough:peak ratio (Figure 4). Furthermore, the 24-h reductions in blood pressure achieved with 10 to 40 mg nisoldipine CC daily are very similar to those seen with 5 to 20 mg lisinopril daily (Figure 5).

CONCLUSIONS

The recent WHO report on Hypertension Control lists specific cases in which monitoring of ambulatory blood pressure may be useful in clinical practice: first, when there is an unusually large discrepancy between blood pressure values measured in the clinic and at home; second, when there is a marked discrepancy between the elevation of blood pressure values and an absence of signs of organ damage; third, when there are marked differences between clinic blood pressure values measured on different occasions; and fourth, when there is resistance to treatment.
Ambulatory blood pressure monitoring will also continue to be used increasingly in clinical pharmacologic and therapeutic research. First, it will be used to provide a more precise assessment of the duration of action and the smoothness of the response to antihypertensive agents. Second, this method will also be useful for dose-finding studies of new compounds, because of the advantage provided by the absence or smallness of the placebo response when ambulatory monitoring is used. Finally, ambulatory blood pressure monitoring will be extremely valuable for further physiological and pathophysiological research, particularly thanks to the advent of new devices, such as the Portapress, allowing noninvasive beat-to-beat monitoring of blood pressure in ambulatory conditions. In the clinical field, as indicated in the WHO/ISH guidelines, “more data are clearly needed on the prognostic significance of blood pressure values obtained by ambulatory blood pressure monitoring or by self-measurements taken at home or at work. The quantification and the prognostic significance of white-coat hypertension (isolated clinic hypertension) should be addressed.”

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