Applications of Ambulatory Blood Pressure Monitoring in Clinical Practice

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Traditionally, blood pressure has been measured by the sphygmomanometer in the medical office. There is growing evidence, however, that office blood pressures may not be typical of values throughout the day. Between 20% and 30% of patients diagnosed with hypertension in the office actually are normotensive at other times. Ambulatory blood pressure monitoring with small, portable devices that automatically measure blood pressure every few minutes throughout the day appears to be an appropriate tool when “white-coat” hypertension is suspected—i.e., for individuals whose hypertension in the physician’s office is not associated with other physical or historical evidence for cardiovascular disease or with other risk factors. Used prudently, ambulatory monitoring is a cost-effective technique that potentially can prevent unnecessary treatment of patients. Moreover, whole-day measurements may correlate more closely than office measurements do with findings of cardiovascular disease. This new approach also has highlighted the circadian pattern of blood pressure, especially the sharp early to mid-morning increase that coincides with an increased tendency to major cardiovascular events. This has focused attention on directing antihypertensive therapy towards the morning hours. Ambulatory monitoring is now used routinely in studies of antihypertensive drugs. This technique has no placebo effect and takes fewer patients to assess drug efficacy than do conventional methods.

Data obtained by conventional sphygmomanometry in the medical clinic or office have been used to define the prognosis and natural history of hypertension. This method of measurement has been used in most of the research studies that have evaluated the pathophysiology of human hypertension or that have been used to assess the response of this disorder to various forms of therapy. Moreover, practicing clinicians use the conventionally measured blood pressure to make a clinical diagnosis of hypertension and reach decisions concerning its treatment. But the sphygmomanometer-measured blood pressure is inconsistent; despite its usefulness in establishing prognostic information in large populations, it can be misleading in the individual patient.

Lightweight, automated, portable monitoring equipment has made it convenient and safe for blood pressure to be measured on a 24-h basis in ambulatory subjects. Studies with this technique have started to establish the role of 24-h blood pressure values in clinical hypertension and to document their relationship to cardiovascular changes. The whole-day blood pressure measured in ambulatory patients correlates more closely than conventional readings with echocardiographically measured indices of cardiac left ventricular muscle mass (1, 2). In turn, this echocardiographic index has been shown to have strong prognostic implications for cardiovascular events (3). Other investigators, using a point-score system based on clinical evaluations of target organ involvement in normotensive and hypertensive patients, have shown that the whole-day blood pressure value is predictive of cardiovascular status (4). The same investigators have shown that blood pressure variability during the day, a measurement that can be derived from whole-day monitoring data, also correlates strongly with the status of the cardiovascular system.

Technology for monitoring blood pressure has not been available long enough to have provided clear data concerning its role in predicting long-term cardiovascular prognosis; however, preliminary studies with semiautomated equipment suggest that this method is superior to conventionally measured blood pressure in forecasting major events (5). Interestingly, a major trial is now underway in Europe to determine the prognostic sensitivity of the ambulatory monitoring technique (6).

At present, the major uses for the whole-day ambulatory blood pressure monitoring appear to be diagnosing hypertension and evaluating responses to treatment, especially the efficacy and duration of action of investigational antihypertensive drugs.

Circadian Pattern of Blood Pressure

Blood pressure follows a characteristic pattern throughout the day. Blood pressure values tend to be at a relatively high plateau during the daytime hours, but then decrease steadily during the evening towards their nadir at midnight or shortly afterwards. Blood pressure then remains low during sleep, but returns sharply to its daytime values during the early to mid-morning hours. The typical blood pressure pattern in normal volunteers is shown in Figure 1 (7). One of the principal determinants of this pattern may be the sympathetic nervous system, because serial measurements of plasma norepinephrine and epinephrine values throughout the day parallel the blood pressure measurements (8). These rapid changes in catecholamines and blood pressure during the morning hours appear to be part of the arousal process and may be of pathophysiological importance. For instance, the incidence of major cardiovascular events, including strokes and myocardial infarctions, is increased at this time of day (9, 10). Studies with ambulatory electrocardiographic monitoring also indicate an increased incidence of myocardial ischemia,
as indicated by ST segment depression, during the morning hours (11).

The importance of blood pressure fluctuations, as documented by simultaneous ambulatory electrocardiographic and blood pressure monitoring, has been demonstrated in studies of myocardial ischemia in patients with known coronary disease (12). Episodes of ST segment depression, either silent or associated with clinical angina, were preceded by evidence for increases in both systolic blood pressure and heart rate. This finding not only casts some light on possible mechanisms associated with myocardial disease but also has implications for the selection of appropriate therapies for treating angina and hypertension. Indeed, awareness of the relationships between blood pressure and acute cardiovascular events has been a stimulus for recent interest in drug formulations that can provide therapeutic effects throughout the full 24 h.

Issues of Diagnosis

Even in carefully performed clinical trials, in which patients have been diagnosed only after several conventional readings were clearly in the hypertensive range, marked placebo responses have brought into question the accuracy of the original diagnoses in many participants (13). Moreover, in as many as 30% of hypertensive patients, blood pressure has remained within the normal range after discontinuation of therapy (14), again indicating that the original diagnosis might have been erroneous.

Physicians customarily delay the diagnosis of hypertension until high blood pressure readings have been confirmed during several office visits. Although this careful approach can help identify some individuals whose initial blood pressure values might have been falsely high, there is growing evidence that blood pressure readings obtained by standard methods often are not truly representative of the blood pressure status throughout the day. We have recently described patients whose blood pressure values during whole-day monitoring were within the normal range despite consistently hypertensive readings during multiple earlier visits to the office, including during a four- to six-week period of placebo treatment (15). Using intra-arterial methods of monitoring, other investigators have observed that the approach of a physician to the patient for the purpose of measuring blood pressure could raise the readings by ~27/14 mmHg (16). Interestingly, this response is not attenuated over time, even after several visits by the physician.

A recent large-scale comparison of hypertensive and normotensive patients has verified that 20% of patients diagnosed as having hypertension by standard clinical means appear normal when evaluated for the full 24-h period (17). Those investigators also found that the high office readings were sustained during multiple visits and concluded that this phenomenon was not one of simple anxiety but instead reflected a conditioned response to the medical environment. They have argued that the doctor–patient relationship might have a unique impact on blood pressure, producing reactions that are not necessarily indicative of responses to other stresses or stimuli during routine daily activities. An experience in our own clinic has verified these findings. As shown in Figure 2, when we compared groups of age- and sex-matched normotensive and hypertensive patients (diagnosed clinically during multiple visits), the
two groups showed a marked overlap in their whole-day systolic and diastolic averages (18).

When Monitoring Is Appropriate?

Obviously, it is not appropriate to perform whole-day automated monitoring of blood pressure in all patients in whom a diagnosis of hypertension is being considered. The decision to diagnose hypertension and administer treatment is readily supported in patients whose high blood pressure readings are associated with clinical or laboratory evidence for target organ involvement. The presence of other cardiovascular risk factors further justifies the prompt treatment of hypertension. Additionally, the presence of a strong family history of hypertension, or possibly of premature cardiovascular disease, encourages the diagnosis and early treatment of hypertension. Thus, the ideal candidate for diagnostic blood pressure monitoring is the patient whose blood pressures are consistently in the mild to moderate hypertensive range and in whom no supportive clinical or historical information favors the diagnosis of hypertension or its need for treatment.

There is no clear agreement on how to interpret the blood pressure monitoring data for diagnoses. One of the simplest methods for analyzing data is to average all readings obtained during the 24 h. This value appears to be a powerful and reproducible reflection of the whole-day blood pressure, provided that the averages are based on readings obtained at consistent intervals throughout the entire period. One can then interpret the whole-day blood pressure value by using diagnostic criteria derived previously from epidemiologic studies with conventionally measured blood pressure. Figure 3, based on observations in 100 subjects, shows a reasonably consistent relationship (for the group as a whole) between office-obtained blood pressures and whole-day blood pressure values (19). Overall, the whole-day blood pressure averages are 10/5 mmHg lower than the office values, presumably because whole-day averages include the lower readings that occur at night. From this, the diagnostic blood pressure criteria of 140/90 mmHg recommended by the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (20) would correspond to whole-day averages of 130/85 mmHg. Standards of the World Health Organization also have been used as a basis for recommending ambulatory blood pressure diagnostic criteria (21). Various statistical approaches for choosing 24-h diagnostic criteria have produced similar diagnostic values (17, 22).

Other approaches to diagnosis also have been recommended, including such observations as the incidence of readings throughout the day that exceed an arbitrary value, or the use of chronobiological concepts such as the hyperbaric index that take into account the actual duration of increases in blood pressure values (23). One can also simply look at the 24-h data and determine, on an empirical basis by clinical experience and judgement, whether there appears to be consistent evidence for hypertension or whether high blood pressure readings can be explained by stimuli or events that occurred during the day.

Controversies

Ambulatory blood pressure monitoring has not yet been universally accepted for the diagnosis of hypertension. One criticism is that "normative" data for blood pressure measured with this method have not yet been established (24). As discussed earlier, at least one major prospective evaluation of ambulatory blood pressure monitoring data is now underway (6). Moreover, based on reviews of the literature involving this technology, some suggestions concerning "normative" data have now been published (25). One could argue that this type of information may not be completely necessary, for there are already abundant epidemiological and actuarial data linking conventional blood pressure values with cardiovascular outcome. Rather, the chief attribute of the whole-day monitoring procedure is to determine whether or not a particular individual patient has a sustained increase in blood pressure. Once that question is answered, then prognostic and therapeutic assumptions can be extrapolated from the established epidemiological experiences.

Some observers have expressed concern at the potential expense of performing numerous monitoring procedures. Thus, as discussed earlier, this technique should be recommended only for those patients in whom the diagnosis of hypertension cannot be established by more standard means. Incidentally, antihypertensive therapy
usually is a lifelong commitment and incurs the expenses of physician visits, clinical tests, medications, and the cost of patients' time lost from work. Even if only a few of the patients studied by the monitoring technique were found not to require therapy, overall we believe this approach would still be cost effective (22, 26).

One important question remains unanswered: Are patients whose conventional blood pressures appear high, but whose 24-h monitoring values fall within the normal range, truly normotensive? Do their higher casual readings, even if they occur only in the physician's office, make them different from individuals whose blood pressures are always normal? In a previous study with standard blood pressure measurements, we subdivided patients into those whose hypertension was sustained during serial clinic visits and those whose blood pressures fell into a borderline or normal range. Measurements by echocardiography of the thickness and muscle mass of the left ventricular wall were virtually identical in the two groups, and were significantly higher in each of them than in normal controls (27). Perhaps the patients with nonsustained hypertension, including those with normal 24-h blood pressure values, might have cardiovascular target organ changes that are typical of true hypertensive disease. This critical issue is the subject of ongoing research.

Application to Treatment

Blood pressure monitoring can be used to study the effectiveness of therapy in individual patients in clinical practice, chiefly in those individuals who do not appear to be responding well to treatment. The interpretation of the findings is somewhat empirical. In one report (28), a group of patients whose blood pressure control in the clinical setting was unsatisfactory were then examined by a monitoring procedure. In some of these patients, the apparently poor response to treatment was confirmed by the monitoring values; in others, the whole-day blood pressure values during treatment were far lower than those observed in the clinic, suggesting that changes in their therapeutic regimens were not required.

The monitoring technique has been used effectively to evaluate new antihypertensive agents (29–34). A strength of this technique is that there is no placebo response, and that determinations of efficacy can be made with fewer patients than would be required if conventional measurements were used (35). Moreover, the power of this technique allows significant differences between different types of treatment to be established in relatively small groups of patients, even when the absolute differences are relatively small (36). Analysis usually is based on comparing blood pressure monitoring values obtained throughout the day during baseline and treatment periods. Comparisons can be based on the blood pressures for the day as a whole or on selected shorter periods. Typically, the day is divided into 12 2-h periods, and the differences between corresponding periods during the pre-treatment and treatment monitoring procedures are assessed statistically. Determining the duration of antihypertensive efficacy is a particular strength of this technique, especially because data can be obtained during sleep and during the critical early morning hours around the time of arousal.

The value of this technique was illustrated in a study in which the effects of an antihypertensive agent given twice daily were compared with its effects when given just once daily (37). We found that the once-daily administration was at least as effective as the twice-daily regimen for the first 20 h of the monitoring period; only near the end of the whole-day observation, during the early morning hours that cannot readily be studied by conventional methods, was there a relative loss of efficacy during the once-daily regimen. An interesting approach to drug evaluation was recently reported with a converting enzyme inhibitor, captopril (38). Whole-day monitoring in the total group of 31 hypertensive patients given this drug once daily indicated a moderate antihypertensive effect. But if patients with relatively poor responses to this treatment (n = 10) were removed from analysis, the data showed that once-daily administration of captopril in the remaining 21 patients provided meaningful antihypertensive efficacy throughout the full 24 h. The key to this important experience was the use of the monitoring technique to focus on the duration of effect in patients already shown to have antihypertensive responses to this drug. A further report focusing on combination drug therapy of hypertension has indicated that drugs that by themselves do not generally provide 24-h efficacy appear to work throughout the day when given in combination (39).

A further illustrative experience has been with the calcium channel blocking agent, diltiazem (40). In 15 patients, all of whom had been shown to have hypertensive blood pressure values by repeated conventional measurements before the start of the study, the administration of diltiazem produced a moderate antihypertensive response that was sustained throughout the full 24 h. However, the baseline blood pressure monitoring procedure performed just before the initiation of therapy indicated that six of the 15 patients failed to meet the criteria for the diagnosis of hypertension (as discussed previously). Analysis of the blood pressure effects of diltiazem in this (nonconfirmed) hypertensive subgroup showed no significant change in their blood pressure with treatment. On the other hand, the monitoring data in the remaining nine truly hypertensive patients indicated that diltiazem produced antihypertensive effects throughout the 24 h that were clearly more powerful than those observed for the treatment group as a whole. By using the diagnostic properties of whole-day monitoring, we could not only determine the efficacy and duration of action of antihypertensive treatment, we could also quantify the effects of treatment in those patients for whom treatment appeared to be most justified.

In conclusion, the technique of automated noninvasive whole-day monitoring of blood pressure clearly is
valuable in the diagnosis of hypertension and in assessing its response to therapy. Further studies in the area of diagnosis are required to more closely link data obtained with the monitoring procedure with the underlying status of the cardiovascular system. We must also study further those patients whose hypertension is not confirmed by the monitoring technique. Are these patients truly normal, or do they have a heightened risk of target organ change? The experiences with ambulatory monitoring in assessing efficacy of antihypertensive treatment have been encouraging, and innovative uses of this method are allowing an improved understanding of new and established antihypertensive agents. This technology will help establish new criteria for characterizing optimal approaches to evaluation and treatment of hypertension.

References