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Assessing hypertension management: the role of 24-hour blood pressure monitoring

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- **BACKGROUND** The first fully automatic portable invasive blood pressure recorder was developed 30 years ago. Today, portable noninvasive ambulatory blood pressure devices are capable of measuring blood pressure intermittently for periods of 24 to 48 hours.
- **OBJECTIVE** To discuss the utility of automatic ambulatory blood pressure recording in assessing antihypertensive therapy.
- **SUMMARY** Ambulatory blood pressure monitoring is helpful in assessing the pharmacodynamics and the clinical efficacy of antihypertensive drugs. It is superior to office blood pressure measurement in predicting hypertensive end-organ disease. In clinical trials, ambulatory blood pressure monitoring permits a more varied population to enter a study, the number of subjects required is often reduced, and a placebo control group may be unnecessary.
- **CONCLUSIONS** The various methods of analyzing ambulatory blood pressure data should be used in a complementary fashion to evaluate antihypertensive drug therapy. We believe that this technique will soon become much more commonly used for hypertension management.

■ INDEX TERMS: BLOOD PRESSURE MONITORS; ANTIHYPERTENSIVE AGENTS
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AMBULATORY BLOOD pressure (BP) monitoring is an important method for assessing the effects of antihypertensive therapy. Besides its use in evaluating the pharmacodynamics of drugs in the patient's usual environment and during various activities, ambulatory BP monitoring is also helpful in assessing their clinical efficacy.

The first fully automatic portable invasive BP recorder was developed by Stott et al¹ 30 years ago. Since then, clever engineering has created portable, noninvasive ambulatory BP devices that are capable of measuring BP intermittently for periods of 24 to 48 hours. Over the past decade, the weight of recorder components, including the motor-driven pump, battery pack, and microprocessors, has been reduced to approximately 1 pound; moreover, the recorders are more user-friendly. For many years, both semiautomatic (the patient initiates the cuff inflation) and automatic devices were marketed; now only automatic recorders are used. This review will discuss the utility of noninvasive, totally automatic ambulatory BP recorders.

The data yielded by ambulatory BP monitors have been of great clinical significance in understanding BP behavior outside the medical care environment.² Ambulatory BP monitoring devices measure the pressure either by oscillometry of pressure waves in the brachial artery or by auscultation of the Korotkoff sounds. At rest, both methods appear precise; during motion or in conditions where there are substantial vibrations (eg, in automobiles), oscillometry may lose precision.³ Most available monitors use Korotkoff sounds to determine BP; some of these devices can also incorporate an algorithm that uses R-wave gating to reduce the signal-to-noise ratio.⁴ Taking the pulse-propagation delay into account and using R-wave gating may improve the accuracy of readings during motion.^{2,4}

THE AMBULATORY BP PROFILE

Data provided by ambulatory BP devices show that BP is characterized by a diurnal (often referred to as circadian) pattern. Two competing theories on the origin of this diurnal rhythm have been described by Pickering⁵: the "set point" model assumes that two tonic levels of BP exist corresponding to waking and sleeping states, whereas the "oscillator" model proposes an intrinsic circadian rhythm determined by time of day and endogenous hormones. Most investigators of ambulatory BP monitoring favor the set point theory, since BP is regularly altered by activity and arousal.⁶ Moreover, the observation that shift workers experience a rapid reversal of the diurnal BP profile (within 1 day) contradicts the oscillatory model.^{6,7}

Ambulatory BP monitoring has clarified that the 24-hour profile in healthy normotensive and hypertensive individuals is characterized by a high span during daytime (waking) hours and a low span after midnight during periods of sleep and inactivity. Typically, nocturnal BP is 10% to 20% below daytime BP; individuals with this pattern have been anecdotally labelled "dippers."⁸ The dipper pattern has been observed in most patients with essential hypertension. A flattened 24-hour BP pattern ("nondipper") occurs in a minority of patients with essential hypertension, in patients with secondary forms of hypertension (including mineralocorticoid-excess syndromes,⁹ pheochromocytoma,¹⁰ and autonomic dysfunction¹¹), and in patients with renal insufficiency.¹² Large doses of corticosteroids or cyclosporine have been reported to alter the

diurnal rhythm of BP in patients who have undergone cardiac transplantation.¹³

The study of diurnal BP variability has opened up a new research discipline. There is much to learn about BP profiles in special populations, including elderly patients, pregnant women, racial groups, patients with a family history of hypertension, and hypertensive patients with concomitant illnesses. Identifying characteristic BP profiles for particular populations is clinically relevant, since patients with persistent elevation of nocturnal pressure may have a greater likelihood of target-organ disease, including left ventricular enlargement.^{14,15}

AMBULATORY BP AND END-ORGAN DISEASE

Extensive reviews have evaluated the relationship of office BP measurement and ambulatory BP monitoring to hypertensive target-organ disease.^{2,16} Most studies have shown that ambulatory BP monitoring is superior to office BP measurement in predicting hypertensive end-organ disease.¹⁶ Although most studies have focused on cardiac consequences of hypertension (eg, left ventricular hypertrophy),^{16,18} some studies have demonstrated that ambulatory BP monitoring is better than office BP measurements in predicting renal abnormalities¹⁹ and cerebrovascular disease.²⁰

Controlled, prospective evaluation of outcome in patients based on ambulatory vs office BP has not been performed. However, Perloff and Sokolow²¹ showed that daytime ambulatory BP monitoring was superior to office BP measurement in predicting cardiovascular morbidity in a treated hypertensive population. This study had several limitations, since the care and follow-up of the patient population was uncontrolled, but it did demonstrate a trend supporting prospective study in borderline and mildly hypertensive patients.

ANALYZING AMBULATORY BP DATA

Ambulatory BP recording produces a substantial amount of data; interpretation of the data is aided by mathematical reduction to values that have clinical relevance.²² The most commonly used methods of data analysis for ambulatory BP monitoring are shown in the *Table*. Typically, several parameters are used to provide the best overall assessment of 24-hour BP.

TABLE
METHODS OF ASSESSING THE EFFECTS
OF ANTIHYPERTENSIVE DRUGS ON AMBULATORY BLOOD PRESSURE

Method	Comment
Evaluation of the 24-hour blood pressure profile Assessment of unsmoothed data (individuals and groups) Assessment of smoothed data (eg, Fourier transforms)	
Mean 24-hour and average awake and sleeping blood pressures	Requires activity monitoring or well-kept activity journals
Median 24-hour waking and sleeping blood pressures	" " "
Blood pressure load	Percentage of pressures > 140/90 mm Hg during waking periods and > 120/80 mm Hg during sleeping periods
Area under the blood pressure curve	Integrated area using same threshold values as the blood pressure load method
Other forms of mathematical modelling Cosinor analysis Spline curves Cusums	

The 24-hour BP profile

The ambulatory BP profile is helpful in assessing the duration of a drug's antihypertensive effect. The pharmacodynamic effect of a drug can be evaluated by using a placebo-subtracted curve: in a placebo-controlled study, the net change in systolic or diastolic BP from a study drug is plotted against the time from dosing. The BP profile reveals the variability of the BP and the possible BP effects of an antihypertensive drug.

If an individual's BP varies widely, the precise hour of peak hemodynamic effects of an antihypertensive agent may be difficult to determine; consequently, some investigators have resorted to data-smoothing techniques such as the Fourier transform,²³ which helps define high and low spans over time. The degree of order (number of harmonics) ascribed to the curve by the Fourier equation affects the shape of the curve: an order of 0 gives a straight line through the data, whereas an order of 10 might yield a curve very similar to the absolute BP values. Usually, an order of 4 or 5 best represents the data of a 24-hour BP curve. Data smoothing or reduction techniques may have some benefits for pharmacodynamic assessment; however, the usefulness of these regression models in clinical medicine has not been determined.

Measures of centrality

The parameters most commonly used to express ambulatory BP data are measures of centrality: the 24-hour mean and the averages of waking and sleeping periods. These values are simple to calculate, and they correlate with hypertensive target-organ disease.^{2,5,14,16} However, mean ambulatory pressure can oversimplify data and be substantially affected by outlying values. Using the median pressure avoids the weight of extreme BP values.

Ambulatory BP load

Ambulatory BP load is another clinically useful parameter. Zachariah et al²⁴ defined the BP load as the number of elevated pressures (> 140/90 mm Hg) over 24 hours divided by the total number of readings obtained. White and Morganroth²⁵ suggested using a different cutoff value (120/80 mm Hg) in sleeping periods, based on observations of normotensive and untreated hypertensive patients. In most mild-to-moderate hypertensive patients, few sleeping BP values exceed 140/90 mm Hg; thus, adopting the higher value for sleeping periods loses the ability to discriminate between normotensive and hypertensive populations. Furthermore, studies using these different waking and sleeping parameters have shown superior correlations with indexes of hypertensive cardiac organ involvement.²⁶

The hypothesis that the BP load predicts cardiac target-organ involvement was evaluated in patients with previously untreated essential hypertension.²⁶ Noninvasive indexes that were studied included the left atrial dimension, left ventricular wall thicknesses and mass index, and systolic and diastolic function. The study found that mean 24-hour BP exceeding 135/80 mm Hg was associated with approximately 70% incidence of abnormal cardiac function or structure, whereas in patients with a mean 24-hour BP under 134/79 mm Hg, the incidence of cardiac target-organ involvement fell to about 15%. When

BP load was correlated with the same cardiac indexes, an even more striking cutoff value for left ventricular abnormalities was observed: at a systolic BP load of 50% or a diastolic BP load of 40% the incidence of an abnormal cardiac index was 85% to 90%, but below these BP load values the incidence fell to about 8%.

Above a certain level of average BP, the BP load plateaus at 100%. Since the risk of cardiovascular morbidity continues to climb as BP rises, BP load does not identify severely hypertensive patients who are at high cardiovascular risk. Incorporating BP load with integration of the area under the BP curve during waking and sleeping periods may overcome this limitation.²⁷

Assessing antihypertensive drugs

During the evaluation of a new antihypertensive agent, the hemodynamic effect of the drug over time (pharmacodynamics) and its efficacy in lowering BP must be determined. In recent years, peak and trough effects have been measured in order to meet specific guidelines of the US Food and Drug Administration (FDA). The peak effect is defined as the greatest reduction in the diastolic or systolic BP during the dosing period; the trough effect is defined as the BP level at the end of the dosing period.²⁸

Based on the peak-trough concept, an antihypertensive drug that produces less than 50% of the peak effect at trough is considered ineffective for that dosing period; a trough effect that exceeds 67% of the peak effect is considered too large and, therefore, unsafe for the dosing period. These values are arbitrary and are based on static measurement of short- and intermediate-acting drugs. New antihypertensive drugs have prolonged half-lives and effective extended-delivery systems, and their trough-peak ratios often exceed 67% without any untoward effects.²²

Ambulatory BP monitoring allows a drug's action

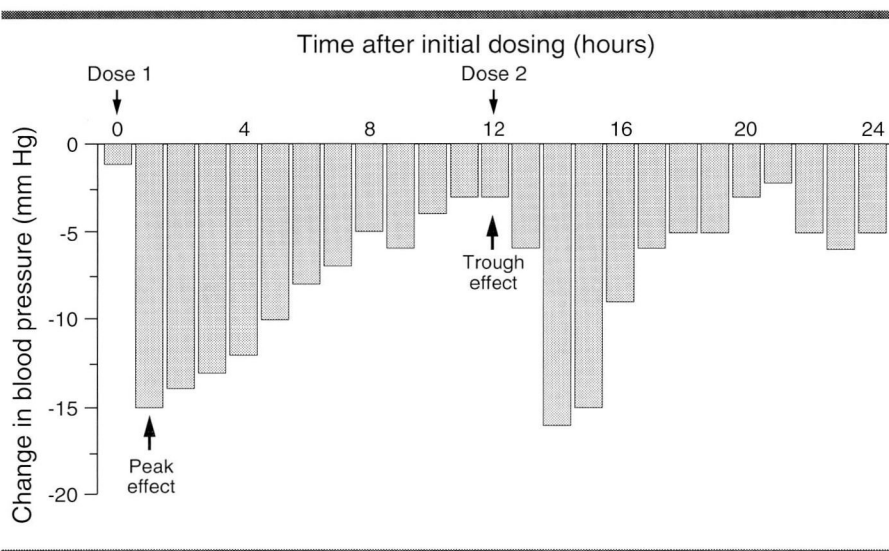


FIGURE 1. Effect on blood pressure of a typical short-acting antihypertensive drug given twice daily. The data are shown as placebo-subtracted hourly blood pressure differences from time of dosing.

to be assessed over time during typical activities of daily living. *Figures 1 to 3* demonstrate hypothetical effects of typical short-, intermediate-, and long-acting antihypertensive agents on ambulatory BP. The data are presented as placebo-subtracted hourly changes. In *Figure 1* and *Figure 2*, the peak and trough effects of a short-acting and intermediate-acting agent are quite discernible; the trough-peak ratio may be calculated directly from these data. In the case of the intermediate-acting drug, which may be approved by the FDA for once- or twice-daily dosing, loss of antihypertensive effect may actually be observed via ambulatory BP monitoring when the drug is administered every 24 hours.

Many drugs with long half-lives or extended-delivery systems show no discernible peak effect after several days of dosing (*Figure 3*).^{22,28} The trough-peak ratio often exceeds 67% and actually may approach 100%. These agents are not associated with untoward effects; in fact, many appear to have fewer adverse side effects than the shorter-acting drugs. For the three drug types, *Figure 3* may illustrate the most desirable pharmacodynamic profile, since increased BP variability is related to enhanced cardiovascular morbidity.^{18,29} The clinical importance of pharmacodynamic profiling may depend on whether reducing BP variability affects cardiovascular morbidity and mortality.

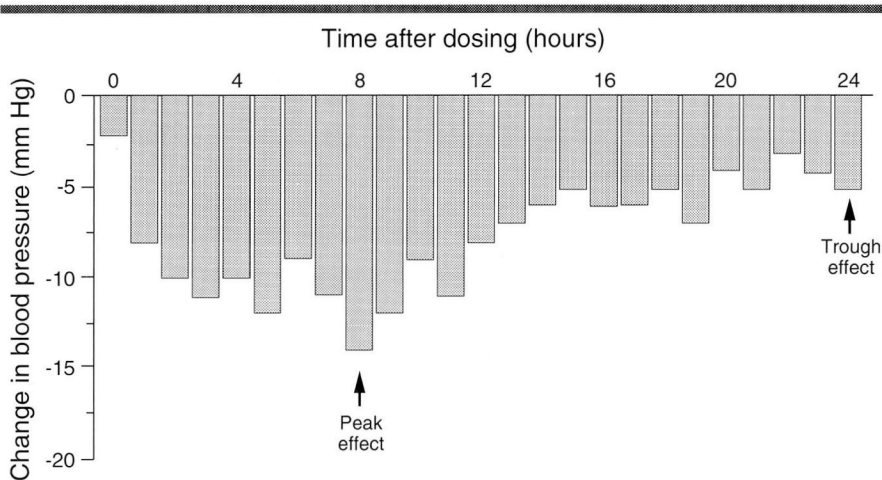


FIGURE 2. Effect on blood pressure of a typical intermediate-acting antihypertensive drug given once daily. The hypotensive effect of the drug attenuates within 12 to 14 hours after dosing.

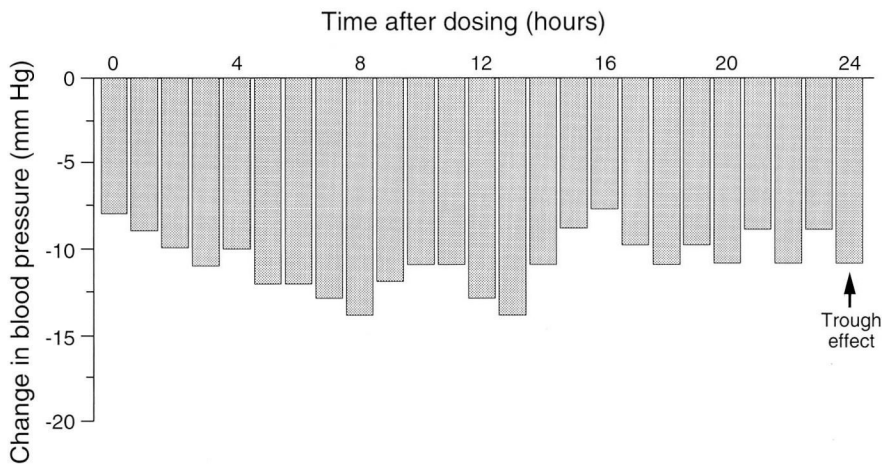


FIGURE 3. Effect on blood pressure of a typical long-acting antihypertensive drug given once daily. After chronic dosing, the peak effect of the agent is indistinct and the trough-peak ratio may approach 1.

AMBULATORY BP MONITORING IN CLINICAL TRIALS

Ambulatory BP monitoring allows all types of patients to participate in clinical trials assessing the pharmacodynamics of new drugs. Without automatic monitoring, patients must spend long periods in clinical research units for repeated BP measurements

to assess peak and trough drug effects; this requirement may induce selection bias into the trial population (eg, a preponderance of unemployed or retired patients). Thus, a more varied population can enter a study, since subjects can participate regardless of age or occupation. Furthermore, the number of subjects required for a study is often reduced, since ambulatory BP varies less than office BP.³⁰ Also, a placebo-control group may be unnecessary, since most studies have shown that while placebo affects office BP levels, 24-hour BP levels are not altered.³⁰⁻³²

Ambulatory BP monitoring avoids some types of errors associated with office BP assessment. Repeated contact with the medical environment, rather than the prescription of a placebo, partially explains the decrease in BP levels observed when patients are evaluated repeatedly by the same clinicians; this alerting response has been recognized for almost 50 years.³³ Reduced BP levels often observed on placebo after several visits in the clinical setting may also be related to the clinician's expectations. This observer bias has been reported even in trained observers involved in nonpharmacologic studies.³⁴ While observer bias and the alerting response do not occur with ambulatory BP monitoring, a prolonged baseline placebo phase is still advisable; this provides the proper amount of time off from antihypertensive therapy, which is needed to obtain precise baseline untreated BP levels.

SUMMARY

Ambulatory BP monitoring is an important tool for evaluating the pharmacodynamics and clinical efficacy of antihypertensive drugs in the patient's usual environment and during various activities. It is superior to clinical BP measurement in predicting hypertensive target-organ disease, since it represents the average daily chronic pressure overload.^{2,16,17,26} The various methods of analyzing ambulatory BP

data—mean 24-hour pressure, BP load, area under the curve—should be used in a complementary fashion to evaluate antihypertensive drug therapy.

Interestingly, physicians in clinical practice have begun to independently order ambulatory BP monitoring not only for diagnostic purposes, but also to assess antihypertensive therapy and refractory hypertension.³⁵ We believe this noninvasive technique will soon become much more commonly used in the management of hypertension.

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