Importance of Blood Pressure Control Over a 24-Hour Period

William B. White, MD

ABSTRACT

BACKGROUND: The circadian rhythm of blood pressure (BP) is associated with a high span during the awake period and a low span during the sleep period. Of interest is that cardiovascular (CV) events occur more frequently in the early morning period, the time when BP and heart rate rise steeply.

OBJECTIVE: To provide an overview of circadian BP and its correlation with adverse clinical outcomes and to discuss strategies for optimizing BP control over 24 hours.

SUMMARY: Patients who have an excessive morning surge in BP and those who lack the normal nocturnal BP fall (nondippers) have been shown to have an excessive incidence of strokes, heart failure, and other CV events. While there are numerous pathophysiologic mechanisms underlying abnormalities in the 24-hour BP profile, including abnormalities in sympathetic nervous system activity, salt and volume balance, and activation of the renin-angiotensin aldosterone system, for many patients the mechanisms remain unclear. Nevertheless, several of these known abnormalities can be modified by clinical interventions, including proper timing of antihypertensive drug therapy and use of classes of antihypertensives for which a substrate exists to induce a pharmacologic effect. It is particularly important to use therapies that will provide control throughout a 24-hour dosing interval.

CONCLUSION: While interventional strategies have not yet been shown to alter clinical outcomes, it is important to be cognizant of their physiologic basis and take them into consideration when making decisions regarding appropriate antihypertensive therapy.

KEYWORDS: Antihypertensive agents; Blood pressure monitoring, ambulatory; Circadian rhythm; Hypertension

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Author

WILLIAM B. WHITE, MD, is a professor, Department of Medicine, and chief, Division of Hypertension and Clinical Pharmacology, Pat and Jim Calhoun Cardiology Center, University of Connecticut Health Center, Farmington. In addition, he is lead physician, Hypertension and Vascular Diseases faculty practice, Cardiology Center, John Dempsey Hospital, and medical director, Clinical Trials Unit, Farmington.

AUTHOR CORRESPONDENCE: William B. White, MD, Division of Hypertension and Clinical Pharmacology, Pat and Jim Calhoun Cardiology Center , University of Connecticut School of Medicine, Farmington, CT 06030-3940; Tel: (860) 679-2104; E-mail: wwhite@nso1.uchc.edu

Arterial blood pressure (BP) has a daily variation characterized by substantial reductions during sleep, a rapid rise upon awakening, and increased variability during the awake period in ambulant normal subjects and hypertensive patients. The patterns of the circadian variation of BP were first established by Millar-Craig et al. using continuous intra-arterial monitoring.[1] This novel study showed that BP was highest in early to mid-morning and then fell progressively throughout the day. In addition, the study showed that BP was lowest at night (nocturnal dip) but rose before awakening (morning surge).[1] These findings demonstrated the potential importance of the circadian rhythm of BP in the management of hypertension, a factor that has been acknowledged since the mid-1960s[2] but did not become part of the clinical hypertension domain until the 21st century.

Following the descriptive findings related to BP variability, researchers began to evaluate the physiologic characteristics that produce the BP rise during the early morning and the substantial BP reductions during sleep. The timing and amplitude of the natural rhythm of BP is influenced by intrinsic factors, such as neurohormonal regulation, but the effects of extrinsic factors, such as physical activity and dietary sodium, may be of greater significance. Additionally, behavioral influences, such as mental activity and emotional state,[3] and lifestyle factors, such as smoking cigarettes and drinking alcohol, can also affect the natural rhythm of BP.[4]

Excessive BP levels during the course of a 24-hour period plausibly contribute to adverse cardiac outcomes, especially when the relationship between the early morning peak in cardiovascular (CV) events with the postawakening morning surge in BP is considered. Increases in the incidence of sudden death, nonfatal myocardial infarction (MI), unstable angina, and stroke in the morning indicate that a patient's physiologic status may play an important role in the onset of CV events.[5] Intuitively, it appears that 24-hour control of BP should have an important clinical impact on the early morning increases in CV events.

Early Morning BP Surge

Blood pressure rises sharply in the morning in response to the activation of the sympathetic nervous system when one arises.[6-10] This early morning surge is associated with other important hemodynamic and neurohormonal changes, including increases in heart rate, vascular tone and blood viscosity, and decreases in vagal activity.[6,11-13] The activity of the sympathetic nervous system is quiescent during sleep, whereas awakening selectively increases epinephrine levels.[8] Subsequent increases in BP and

heart rate are controlled by direct sympathetic neural input into the heart and vasculature in response to increases in activity and upright posture, rather than by an endogenous surge of plasma catecholamines.[9]

Nondippers—The Loss of the Nocturnal Decline in BP

The normal circadian rhythm of BP has a nocturnal decrease of 15% to 25% in BP compared with awake values. However, in 25% to 40% of patients with hypertension, a "nondipper" pattern is present. Since the 1980s, the nondipping pattern has been arbitrarily defined as when the BP reduction during sleep is less than 10% compared with BP while awake. Blunting of the nocturnal decrease in BP in patients with hypertension occurs for a variety of reasons, both in patients with essential hypertension and with secondary forms of hypertension. Clinical studies in patients with hypertension have found that a blunted nocturnal BP decrease occurs when there is an increase in adrenergic activity and a decrease in vagal activity during sleep.[14-16] In some patients, there is even a significant increase in BP during sleep (and in the supine position), which leads to a "reverse dippers" or "riser" pattern—a finding that is associated with substantial cardiac morbidity.[17] Japanese investigators also reported that a profile in which the nocturnal BP is >20% less than the awake BP has been associated with increased white matter ischemic lesions in the brain.[17] Thus, knowledge of the circadian profile of an individual patient (through 24-hour ambulatory BP monitoring) with hypertension may aid in identifying increased risk.

Clinical Implications of the Circadian Variability of BP

As stated above, the early morning BP surge is associated with an increase in the incidence of CV events, including stroke and MI.[18-20] Pooled analyses of event data indicate that there is a 40% higher relative risk of acute MI, a 29% increased risk of sudden cardiac death, and a 49% higher relative risk of stroke between 6 a.m. and noon than during the rest of the day.[19,20] In actual terms, this corresponds to approximately 1 in 11 MIs, 1 in 15 sudden deaths, and 1 in 8 strokes occurring in the early morning period when BP, heart rate, and the rate-pressure product increases most steeply.[19,20]

For many years, epidemiologic studies have shown that the timing of onset of CV events strongly parallels the circadian rhythm of BP. In an interesting analysis in Japan, Kario et al.[21] demonstrated a 2.7-fold increase in the risk of a future stroke in older patients with hypertension who were in the top decile of the morning BP surge (>34 mm Hg; Table). For each 10 mm Hg increase in the morning BP surge, there was a 24% increase in stroke risk ($P=0.004$). While it would be of great interest to perform a clinical trial devised to address the relationship between a reduction in the early morning BP and a possible reduction in CV events, this is unlikely to occur because of the enormous sample size required and the long period of follow-up that would be necessary.[22]

TABLE Correlation Between Morning Blood Pressure Surge and Cardiovascular Events[21]

	AM Surge (n = 53)	Non-Surge (n = 466)
Baseline data		
Silent ischemic infarcts		
Prevalence (%)	70†	48
Average number	2.3 ± 2.6	13 ± 2.6
Multiple ischemic infarcts		
Prevalence (%)	57*	33
Prospective data		
Ischemic strokes (%)	19.0†	7.3

*$P<0.001$.

†$P<0.01$.

Loss of the nocturnal decline in BP has been associated with increased risk of cardiac, kidney, and vascular target-organ injury compared with patients whose decline in BP at night is normal,[23] and can be independent of the clinic and 24-hour mean BP values.[24,25] Additionally, patients with hypertension who exhibit a nocturnal BP increase compared with daytime BP (risers) have the worst prognosis for stroke and cardiac events.[17,24] However, there is also some evidence that patients with marked nocturnal BP declines (extreme dippers) are at risk of lacunar strokes and silent myocardial ischemia.[26]

Clinical Factors That Affect the Circadian Rhythm of BP

Physical activity is the major determinant of BP rise during the day.[25,27] As mentioned earlier, the influence of sleep and wakefulness on BP is mediated through cyclic variations of the autonomic nervous system. In the early morning, BP naturally rises sharply in response to activation of the sympathetic nervous system upon arousal.[4,6,8] Sleep deprivation increases sympathetic activity and may disrupt circadian rhythmicity. The circadian BP rhythm—in particular, the nocturnal decline in BP—can be affected by sodium intake in patients with hypertension.[28] In fact, Uzu et al.[29] showed that a nondipper nocturnal BP pattern can be converted to a dipper pattern in response to salt restriction in salt-sensitive patients with hypertension.

The renin-angiotensin aldosterone system (RAAS), mainly via production of angiotensin II (Ang II), is a key regulator of BP. Renin secretion is activated in the early morning before arousal as a result of sympathetic neuronal activation.[30,31] In addition, both renin and aldosterone demonstrate significant circadian patterns in both normotensive and hypertensive individuals,[31] with peak values detected early morning, then falling to their lowest point in late evening (Figure 1).[32,33] A similar pattern has been observed for Ang II.[30]

FIGURE 1 The Circadian Variation of Blood Pressure (BP) Hemodynamics, Electrolytes, and Neurohomonal Systems.[33]

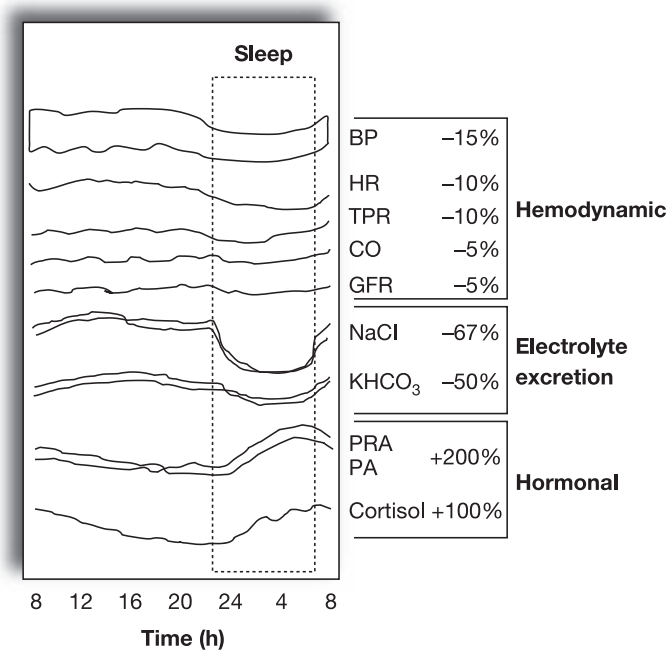

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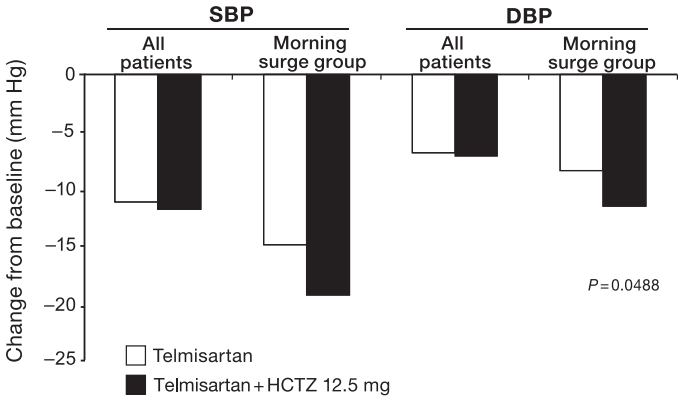
FIGURE 2 Reductions in Early Morning Blood Pressure (BP) from the MICCAT-2 Trial[36]



Patients with an early morning surge (>30 mm Hg systolic BP) showed larger reductions in ambulatory BP compared with those lacking an early morning surge. DBP=diastolic blood pressure; SBP=systolic blood pressure. Adapted from White WB et al. Blood Press Monit. *2005;10:157-63 with permission.*

How Antihypertensive Therapies Affect the 24-Hour Blood Pressure Based on the Pathophysiology of the Circadian Rhythm

The morning surge in hypertension, which is associated with increases in stroke events in older patients with hypertension, is mediated in part by the sympathetic nervous system and through the RAAS. A loss of decline in nocturnal BP is probably mediated through both RAAS activation and volume excess. These findings have led to the evaluation of the potential for blockade of the systems that lead to these abnormal profiles in circadian BP. Notwithstanding, the pharmacodynamics of antihypertensive drugs must play a role here, since control of nocturnal BP and BP during the early morning period will require that agents either have a reasonably long half-life or else be administered twice daily.

Modification of the timing of drug administration can alter the circadian BP profile. In fact, modification of the time of drug administration for many of the antihypertensive agents may affect the extent of 24-hour BP control and modify the circadian rhythm, including the conversion from a nondipper to a dipper profile.[34,35] These effects are most uniform with blockers of the RAAS, which typically will have a substantial effect on nocturnal BP when they are administered at night while also maintaining adequate control during the daytime.[35]

Drugs with long duration of action may be particularly useful for blunting the early morning surge in BP. White et al.[36] evaluated the effects of telmisartan alone and in combination with hydrochlorothiazide (HCTZ) on 24-hour BP, including the early morning period (Figure 2). Patients with hypertension received telmisartan 40 mg per day. If BP remained uncontrolled after 2 weeks, the dose was increased to 80 mg per day; if BP was still uncontrolled after another 4 weeks, HCTZ 12.5 mg was added and continued for a final 4-week period. Twenty-four-hour ambulatory BP monitoring was performed at baseline and at the end of the treatment period in 1,628 patients. Telmisartan alone and in combination with HCTZ produced significant reductions in both daytime and nighttime mean BP. The effect was more dramatic in patients with early morning surges, as shown in Figure 2.

Since most analyses have shown that renin activity begins to rise during the night and peaks in the morning period (Figure 1), another pharmacologic approach to consider in the treatment of nocturnal and early morning hypertension would be a long-acting direct renin inhibitor (DRI). Stanton et al.[37] have provided data supporting the concept that aliskiren, a DRI with a plasma half-life of approximately 25-30 hours, might provide efficacy in patients with abnormal circadian BP variability, particularly in the high-risk populations discussed here (Figure 3). In this early trial of the agent, intermediate and higher doses (150 mg and 300 mg) were assessed in a trial compared with high-dose losartan (100 mg daily) and placebo.

As noted, the reductions in nocturnal BP were substantial with aliskiren 300 mg daily (Figure 3) and occurred when renin secretion begins to peak. Oh et al.[38] also reported the results of a trial in 216 patients with hypertension who were randomized to 8 weeks' treatment with aliskiren 150 mg, 300 mg, or 600 mg once daily or with placebo. Aliskiren significantly reduced mean 24-hour ambulatory BP compared with placebo at all dosages. Consistent with its long pharmacologic half-life, aliskiren effectively lowered BP throughout the 24-hour dosing period, persisting overnight and throughout the high-risk period in the early hours of the morning. Furthermore, no rebound effect was seen in this study after withdrawal of aliskiren.

Perhaps the most important clinical benefit of ambulatory BP monitoring in patients with hypertension and comorbid illnesses is to confirm that these patients have adequate control over a 24-hour period (Figure 4). Additionally, while there are potential benefits of conversion of a nondipping pattern to a dipping pattern, the possibility remains that excessive BP reduction at night might be associated with orthostatic hypotension or excessive hypotension during sleep in certain individuals, particularly the elderly.[28,39] Ideally, changes in drug administration time could be followed by repeat ambulatory BP monitoring to assess the effects of therapy and rule out an excessive BP fall during the night.[39] However, this practice is not likely to be covered by most third-party insurance payers. An alternative is to perform 1 ambulatory BP study that is paired with frequent self- or home BP measurement in order to obtain a frame of reference for future patient assessment using home BP measurements.

Conclusions

The importance of adequate BP control over the entire 24-hour period, particularly the early morning hours, cannot be overemphasized. Several of the pathophysiologic systems responsible for the circadian BP variability, especially salt balance and the RAAS, can be modulated by appropriate, long-acting therapy, and such interventions may result in improved clinical outcomes.

The confirmation that correcting 24-hour BP profiles results in clinical outcomes benefit will require clinical trials that specifically test this hypothesis. One example would be studies in which patients are randomized to different drug-dosing schedules with efficacy confirmed by sequential ambulatory BP monitoring versus standard office measurements. These outcomes could be initially composed of surrogate measures, such as changes in left ventricular hypertrophy, vascular structure and function, ischemic brain lesions, or proteinuria. If they suggest benefits, then large-scale studies with conventional CV endpoints would be justified and helpful for determining precisely when to use ambulatory BP monitoring in the clinical management of patients with hypertension.

DISCLOSURES

The author has served as a consultant to Boehringer and Novartis.

FIGURE 3 Effects of the Direct Renin Inhibitor Aliskiren and the Angiotensin II Receptor Blocker Losartan Versus Placebo on Baseline 24-Hour Systolic Blood Pressure (BP) Profiles.[37]

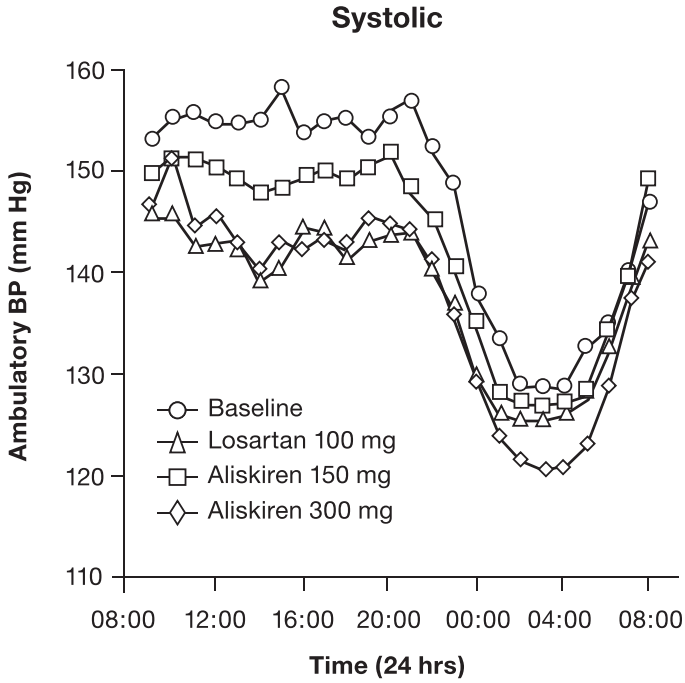


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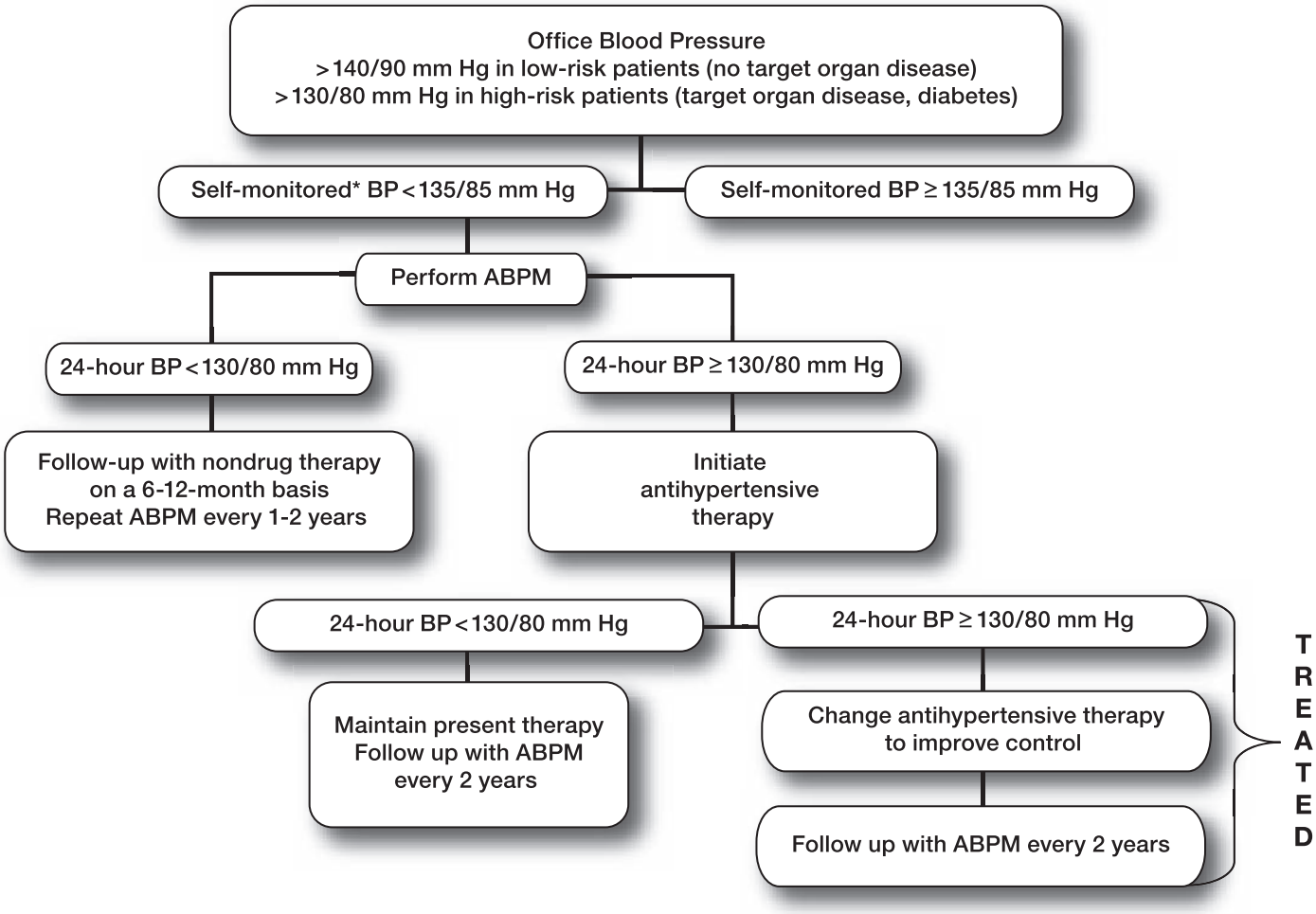
FIGURE 4 An Algorithm for the Utility of Ambulatory Blood Pressure (BP) Monitoring in Clinical Practice.[39]



**Self-monitoring of blood pressure should include at least 1 week of recording by the patient twice each day at home, in the work environment, or both.*
ABPM=ambulatory blood pressure monitoring.

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