Circadian Variations in Cardiovascular Disease: Chronotherapeutic Approaches to the Management of Hypertension

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Blood pressure (BP) exhibits strong circadian variation, and this variation may contribute to the increase of acute cardiovascular events that peak in the morning hours. Reducing morning BP may prevent these occurrences, so identifying data on the true duration of action of antihypertensive agents is essential. Ambulatory BP monitoring has uncovered important differences in commonly used once-daily therapies and has provided insights into the cardiovascular risks associated with BP variability. This article will explore chronotherapeutic antihypertensive agents that have been formulated to address the circadian challenges in controlling BP, and will consider the implications of chronotherapeutics in managing cardiovascular disease.
[Rev Cardiovasc Med. *2004;5(3):148-155*]

Key words: Hypertension • Blood pressure • Chronotherapy • Ambulatory blood pressure monitoring

Circadian rhythms—the body's 24-hour pattern of cyclical activity—have attracted attention for many years, most frequently with respect to the human sleep-wake cycle. A number of reports have also detailed the impact of circadian variations on blood pressure (BP). BP levels follow a typical pattern: they are highest in the early morning and then decline to a trough value after midnight.[1–3] Cardiovascular events, such as myocardial infarction (MI),

ischemia, sudden cardiac death, and stroke, appear to follow a similar pattern, being most common in the early part of the day.[4–12] Therefore, there exists much interest in the potential connection between the cyclical nature of BP and its effects on the cardiovascular system.

Given that the onset of cardiovascular events may follow a circadian pattern, clinicians have begun to reassess treatment approaches. An interesting new development in the management of cardiovascular disease is chronotherapy. This approach bases treatment on circadian variations so that the desired pharmacologic effects of drugs are enhanced, and unwanted outcomes are diminished. Hypertension is 1 example of a disease state in which this approach has been utilized. Innovative formulations have transformed some established antihypertensive agents into newer treatments designed to optimize BP control throughout the day, with maximal blood pressure reductions during the early morning hours.

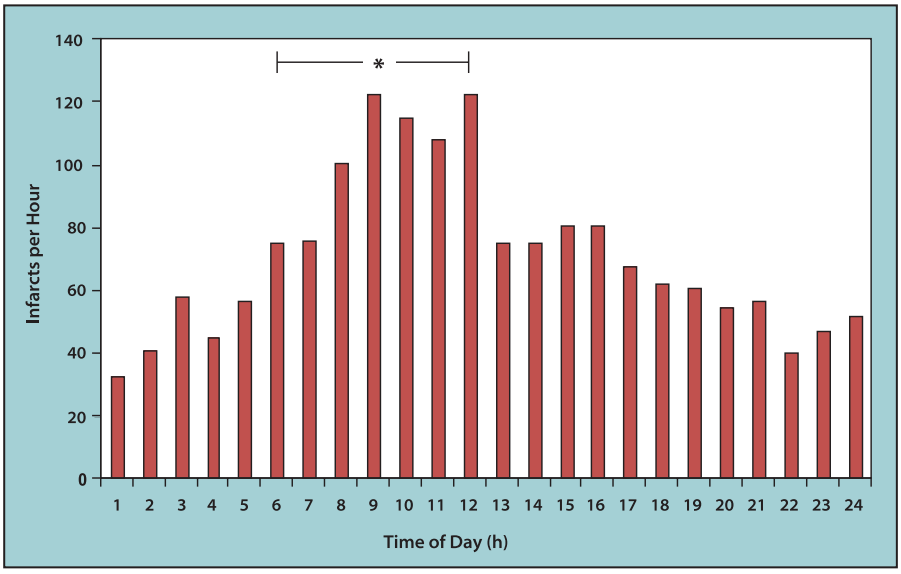

Figure 1. *Incidence of myocardial infarction in the ISAM study. The high incidence of cardiovascular events in the early morning hours is marked.* Adapted with permission from Willich et al.*[5] www.medreviews.com

Cardiovascular Events Are Most Common During the Early Morning Hours

Several large epidemiological studies have documented that adverse cardiovascular events demonstrate an uneven circadian periodicity, with peak incidence during the hours after awakening. For example, researchers with the Multicenter Investigation of Limitation of Infarct Size (MILIS) analyzed the onset of pain in an extensive database of patients suspected of having MI.[4] The timing of the onset of pain peaked between the hours of 6 AM and noon, suggesting a circadian pattern for MI. Objective evidence supported these findings, with a strong and significant correlation between the onset of MI, estimated by plasma creatine kinase-MB (CK-MB) levels and by pain. An analysis of data from the multinational Intravenous Streptokinase in Acute Myocardial infarction (ISAM) study also demonstrated a circadian pattern in the incidence of MI (see Figure 1). Researchers who timed the occurrence of MI, based on the commencement of clinical symptoms, found a significantly greater incidence between the hours of 6 AM and noon in comparison to other periods of the day. As in MILIS, the enzyme changes confirmed the early morning increases in cardiovascular events.[5] Other studies that used only onset of pain as a marker for MI also supported these findings.[6,7]

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Evidence also exists for a circadian variation in the occurrence of sudden cardiac death. The Massachusetts Death Certificate Study analyzed 2203 death certificates of individuals who experienced out-of-hospital, sudden cardiac deaths. The results indicated a circadian pattern, with strong clustering occurring between 7 AM and 11 AM.[8] Consistent with this finding were the results of a prospectively defined analysis that investigated the time of sudden cardiac death of the original cohort (N = 5209) enrolled in the Framingham Heart Study.[9] Deaths in hospitalized or bedridden patients, or those occurring within 1 month of a documented MI, were excluded from analysis. The time of death, identified for 59% of the 429 definite or possible sudden cardiac deaths, was significantly more likely to occur between 6 AM and noon than during any other time of day. In fact, the risk of sudden cardiac death was approximately 70% higher between the hours of 7 AM and 9 AM versus the average risk at other periods during the day.

The relationship between time of day and occurrence of stroke appears to be similar to that observed for MI and sudden cardiac death. A large study conducted by Marler and colleagues[10] investigated the frequency of ischemic strokes during 2-hour intervals in 1167 patients. More strokes occurred (in patients who were awake) between the hours of 10 AM and noon than during any other 2-hour period. Similarly, Argentino and colleagues[11] studied 426 patients within 12 hours of the onset of hemispheric stroke and found that 56% of all events occurred between 6 AM and noon.

A recent evaluation of cardiovascular episodes and their timing by Elliott[12] described meta-analyses that verified a 40% higher risk of heart attack, a 29% higher risk of cardiac death, and a 49% higher risk of all types of strokes during the critical hours between 6 AM and noon than during the remainder of the 24-hour period. Taken together, and similar to the morning BP surge, cardiovascular events have a circadian pattern of occurrence and are more likely to occur during the early part of the day. Moreover, it has been postulated that the onset of cardiovascular events is stimulated by the physiologic phenomena that occur upon arising from sleep and is not merely a function of the time of day.

Can the Characteristic Pattern of Blood Pressure Explain These Clinical Findings?

The dynamics of awakening or arousal, including commencement of physical activity, precipitate a cascade effect. Morning increases in the sympathetic system as reflected in elevated catecholamine levels, specifically norepinephrine and epinephrine, as well as heightened activity in the renin-angiotensin-aldosterone system, may alter the body's hemodynamic forces.[3,13] These changes result in elevations in BP (about 3 mm Hg/h for systolic BP and 2 mm Hg/h for diastolic BP during a 4- to 6-hour period upon awakening), heart rate, cardiac output, peripheral resistance, myocardial contractility, and, ultimately, myocardial oxygen demand.[3,13] These stressors may place predisposed individuals at risk for rupture of atherosclerotic plaques.[13] At the same time, increases in platelet aggregability, blood viscosity, fibrinolytic activity, and vascular tone have the potential to promote the formation of intraluminal thrombi, the presence of which in the coronary circulation could create increased myocardial vulnerability.[13,14] Individuals with established hypertension, cardiovascular disease, and related disorders are less likely to tolerate these changes, and therefore it should be no surprise that they are more prone to myocardial ischemia, MI, stroke, and sudden cardiac death during the period of awakening. These findings suggest that modification of certain triggers could reduce the probability of adverse cardiovascular events. Because elevated BP has been linked to the development of cardiovascular disease, it has been postulated that the surge in morning BP is a contributing factor to the expanded incidence of cardiovascular events at that time.

In a preliminary investigation of this relationship, 237 hypertensive patients without previous events were followed for 5 years or more. Only 23 of these patients developed signs of cardiovascular complications.[15] Nonetheless, when the cohort was divided according to quartiles of systolic BP upon arising, the incidence of events was highest in the group with the most elevated systolic BP upon rising (153–231 mm Hg). This small study appears to support the importance of early morning BP as a predictor of cardiovascular outcomes.

Consistent with this view, a newly published report has confirmed the independent association between excessive elevations in morning BP and the risk of stroke in elderly hypertensive patients.[16] Researchers prospectively followed 519 patients for an average of 41 months, during which 44 strokes occurred. Those patients with a morning BP surge in the highest quartile (≥ 55 mm Hg) had a higher incidence of stroke during the follow-up period in comparison to the other patients (19% vs 7.3%), as well as a significantly greater prevalence of baseline multiple cerebral infarcts as measured by magnetic resonance imaging (57% vs 33%).

Inevitably, there has been considerable interest regarding the possible benefits of targeted BP lowering during the early morning hours. Although not designed to evaluate this particular endpoint, the Heart Outcomes Prevention Evaluation (HOPE) trial studied the administration of the angiotensin-converting enzyme (ACE) inhibitor ramipril dosed at night and demonstrated favorable effects on cardiovascular morbidity and mortality in patients at high risk for cardiovascular events.[17] In this study, due to apparently small reductions in BP, the authors attributed the reduction in cardiovascular outcomes to nonhemodynamic mechanisms of ACE inhibition. But, interestingly, a small substudy using ambulatory BP monitoring, an automated technique that provides multiple measurements of BP on a 24-hour basis, showed that ramipril produced a strong antihypertensive effect during the night (as opposed to a minimal daytime effect), a finding that could be consistent with early morning clinical outcomes benefits.[18] Further studies would be required to test this hypothesis.

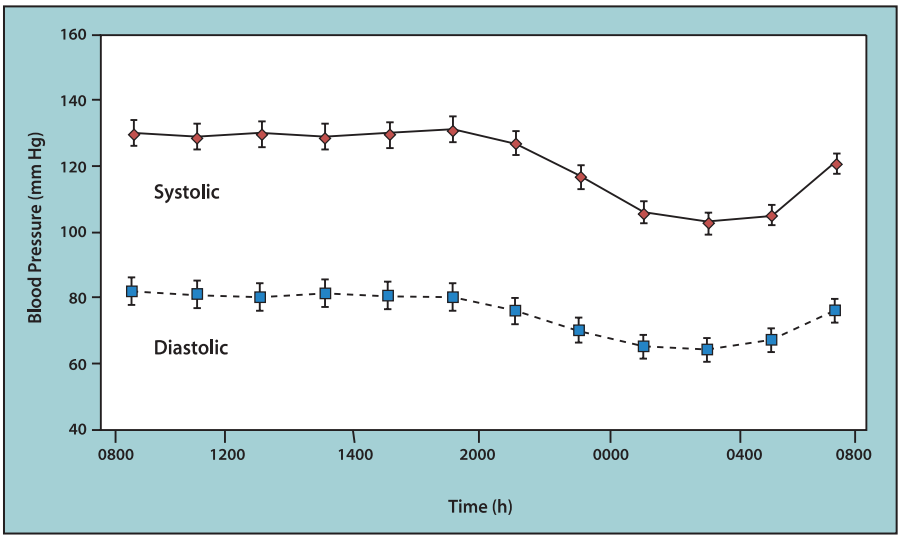

Figure 2. *Typical 24-hour circadian pattern of BP in a normotensive individual. Reproduced with permission from Neutel et al.*[21] www.medreviews.com

Ambulatory Blood Pressure Monitoring: Improving Standards in Evaluating Blood Pressure Control

Ambulatory blood pressure monitoring allows researchers to produce accurate and reproducible data on the circadian pattern of blood pressure as well as the efficacy and duration of action of antihypertensive agents.[19–21] Studies monitoring the 24-hour BP profiles of normotensive patients have confirmed the characteristic circadian pattern of morning elevations and nighttime reductions in BP (see Figure 2). Moreover, accumulating evidence from ambulatory blood pressure monitoring studies suggests that the rapid increase in BP during arousal from sleep has an important role in precipitating early morning cardiovascular events. For example, in a study conducted by Deedwania and colleagues,[22] patients with chronic angina undergoing simultaneous ambulatory blood pressure monitoring and Holter monitoring display a close relationship between BP increases, at any time of the day, and documented episodes of silent ischemia. Patients in this study typically experienced a surge in BP on the ambulatory blood pressure monitor, followed by a significant episode of silent ischemia demonstrated by clinically significant ST-segment depression. Results of the ambulatory study of the Systolic Hypertension in Europe (SYST-Eur) trial,[23] which compared the prognostic significance of conventional and ambulatory BP measurements, showed that ambulatory systolic BP was a significant predictor of cardiovascular risk in untreated hypertensive patients. Importantly, a recent study by Clement and coworkers[24] demonstrated that 24-hour ambulatory blood pressure monitoring can also provide prognostic information concerning cardiovascular events in treated patients with hypertension. In this study, individuals with a mean 24-hour systolic BP of 135 mm Hg or higher were almost twice as likely to experience a cardiovascular event as those with a mean 24-hour systolic BP less than 135 mm Hg, even after adjusting for office measurements of BP.

The use of ambulatory BP monitoring has also uncovered valuable information regarding differences in 24-hour efficacy of once-daily antihypertensive agents. Studies using conventional BP measuring techniques generally record morning trough BP levels (immediately before the next dose is due) and calculate trough-to-peak ratios (where peak is the maximum drug effect) as a marker for 24-hour antihypertensive efficacy (Figure 2); drugs with a trough-to-peak ratio greater than 50% are typically given once-a-day indications. However, the use of standard clinical measurements to assess antihypertensive efficacy can be misleading. A study evaluating once-daily treatment with either atenolol (50–100 mg) or bisoprolol (10–20 mg) provided similar reductions in office BP measurements. But when the drugs were compared using 24-hour ambulatory BP monitoring, bisoprolol was shown to reduce whole-day diastolic BP 33% more than atenolol.[25] Bisoprolol also maintained significantly greater BP control during the final 4 hours of the dosing interval compared with atenolol (see Table 1). Other ambulatory BP monitoring studies suggest similar inconsistencies in the 24-hour control of BP among various once-daily antihypertensive agents.[26,27] Given the growing evidence suggesting the importance of adequate BP control during the early morning hours, it has become increasingly important to provide physicians with data on the true duration of action of various antihypertensive agents. Consequently, newer antihypertensive formulations, designed to address 24-hour BP variations, with greater BP-lowering effects during the early morning hours, are being introduced.

Novel Therapies: A Step Closer to Addressing the Morning Rise in Blood Pressure

Reformulating a conventional drug so that its release into the blood-

stream is timed to coincide with the early morning BP spike is the premise behind recent additions to the antihypertensive armamentarium. Currently, 2 nondihydropyridine calcium channel blockers (CCBs) (verapamil and diltiazem) and 1 ß-blocker (propranolol) are available in such formulations. The CCBs include Covera-HS® (Pfizer Inc., New York, NY), which distributes verapamil using a controlled-onset, extended-release (COER) delivery system; Verelan® PM (Schwarz Pharma, Inc., Mequon, WI), which uses chronotherapeutic oral drug absorption system (CODAS) technology to release verapamil; and Cardizem® LA (Biovail Corporation, Mississauga, Ontario, Canada), a graded-extended-release formulation of diltiazem that utilizes a wax bead matrix system to deliver the active drug. A bedtime-dosed, extended-release formulation of propranolol (InnoPran XL™, Reliant Pharmaceuticals, Liberty Corner, NJ) is the only such ß-blocker available. Nocturnal dosing of these agents not only provides 24-hour BP control, but also releases the drug in such a way that the greatest BP reductions occur in the critical early morning hours, when the majority of cardiovascular events occur.

Several studies have evaluated the BP-lowering effects of these chronotherapeutic, antihypertensive agents.[28–35] Smith and colleagues[28] studied various evening doses of the CODAS-verapamil delivery system and found that doses of 200 mg or more produced continuous BP control over 24 hours, with maximum reductions between 6 AM and noon. Similarly, a study assessing BP control at various critical times during a 24-hour period after administration of 240 mg of COER-verapamil also described BP reductions that were sustained throughout 24 hours with maximal reductions achieved in the early morning.[29] An analysis by Glasser and colleagues[31] comparing nighttime versus morning administration of graded-extended-release diltiazem demonstrated enhanced efficacy in the critical 6 AM-to-noon period when the drug was administered in the evening. All patients given the graded-extended-release diltiazem formulation experienced mean reductions in diastolic BP from baseline, but patients treated with the 360 mg evening dose had a greater decrease than those treated with the 360 mg morning dose (-3.30 mm Hg treatment difference). Recently, Sica and coworkers[32] published a study comparing bedtime dosing of sustained-release propranolol to a novel chronotherapeutic formulation (propranolol CR) of the drug. The authors found that release and absorption of propranolol CR was delayed about 4 hours, after which plasma levels steadily increased to their highest levels at about 10 AM, a time coinciding with the peak morning BP elevations as well as cardiovascular vulnerability. In contrast, plasma levels of the older sustained-release propranolol began to rise immediately following dosing and typically reached a plateau between 4 AM and 10 AM.

Taken together, these data indicate that nighttime administration of chronotherapeutic antihypertensive agents provides efficient lowering of BP during the potentially dangerous morning hours (see Figure 3). However, it is not entirely clear if these agents are superior to the conventional morning dosing of traditional antihypertensive therapies. White and colleagues[33] assessed differences in the effects of bedtime administered COER-verapamil and a conventional once-a-day controlled-release nifedipine formulation (Procardia XL®, Pfizer Inc., New York, NY) dosed in the morning and reported equivalent changes in early morning BP, although COER-verapamil had greater effects on early morning hemodynamic measures (heart rate, heart rate-systolic BP product, and rate of rise of BP) and lesser effects during sleep. Newly published reports by White and colleagues[34] and Bakris and colleagues[35] studied the chronotherapeutic effects of COER-verapamil for the control of early morning BP, comparing its nighttime dosing with morning administration of enalapril (Vasotec®, Merck & Co., Inc., Whitehouse Station, NJ) and

Table 1
Effects of Bisoprolol and Atenolol on Systolic and Diastolic BP over Defined Time Intervals of the 24-hour Monitoring Period

	Mean Change in Systolic BP (mm Hg)			Mean Change in Diastolic BP (mm Hg)		
Time Interval	Bisoprolol	Atenolol	*P* Value	Bisoprolol	Atenolol	*P* Value
6 AM–10 PM	–16.5	–12.4	= .03	–12.8	–8.9	< .001
6 AM–noon	–14.2	–9.9	= .03	–11.5	–7.7	< .01
10 PM–6 AM	–12.2	–10.9	= .54	–9.6	–8.5	= .41
Last 4 hours of dosing interval (6 AM–10 AM)	–13.2	–8.9	< .05	–10.9	–7.3	< .01

Data from Neutel et al.[25]

Figure 3. *Ambulatory diastolic BP profiles produced by bedtime dosing of* **(A)** *COER-verapamil (Covera-HS®); data from Neutel et al.*[29] **(B)** *CODAS-verapamil (Verelan® PM); adapted with permission from Smith et al.*[28] **(C)** *Graded-extended-release diltiazem (Cardizem® LA); adapted with permission from Glasser et al.*[31]

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losartan (Cozaar®, Merck & Co., Inc., Whitehouse Station, NJ). In these 8-week forced-titration trials, COER-verapamil was more effective at lowering early morning BP. White and colleagues[34] evaluated measurements at 4 weeks, and COER-verapamil reduced 4-hour, postawakening morning BP (-11.2/-7.5 mm Hg) to a greater extent than did either conventional agent: enalapril lowered target BP rates by 6.0/4.3 mm Hg, and losartan caused reductions of 5.7/3.8 mm Hg. Similar but larger reductions (due to higher doses of the various treatments) were observed after 8 weeks of treatment. Comparable BP reductions were reported by Bakris and colleagues[35] after 8 weeks: morning BP was lowered by 16.6/11.9 mm Hg for COER-verapamil, 10.4/6.0 mm Hg for enalapril, and 8.9/5.2 mm Hg for losartan. Moreover, in each of the studies, COER-verapamil consistently lowered the rate-pressure product—a measure of myocardial oxygen demand—by a larger magnitude than enalapril or losartan in the early morning and throughout the 24-hour period.

It should be noted, however, that further studies are needed to evaluate whether chronotherapeutic agents are superior to other standard BP therapies in preventing cardiovascular events. Certainly, there are some new drugs with particularly long plasma half-lives that do provide meaningful antihypertensive efficacy during the full 24-hour dosing interval.[36] The circadian relationship between morning BP and cardiovascular events was going to be addressed in the recently published Controlled ONset Verapamil INvestigation of Cardiovascular Endpoint (CONVINCE) trial,[37] a study designed to compare 2 initial hypertensive treatments (monotherapy with COER-verapamil [Covera-HS®] and a physi-

cian-directed choice of the diuretic hydrochlorothiazide [HCTZ] or the ß-blocker atenolol). The established combined primary endpoint was fatal or nonfatal MI, fatal or nonfatal stroke, or cardiovascular death.[37] CONVINCE was originally designed to allow for a 5-year follow-up, which would have included evaluation of several secondary endpoints. Of particular interest was the impact of nighttime administration of COER-verapamil on the incidence of cardiovascular events occurring between the hours of 6 AM and noon. Unfortunately, the study was terminated early for financial reasons by the pharmaceutical sponsor and was unable to meet these goals. Although only 3 years of follow-up were available, thus preventing investigators from establishing the efficacy of chronotherapy, CONVINCE did confirm previous findings regarding the chronobiology of cardiovascular events. Still, the early termination of the study further emphasizes the need for continued research concerning (1) chronotherapeutic antihypertensive therapy and (2) the relationship between the early morning BP surge and the increased incidence of cardiovascular events that occur upon awakening.

Conclusions

BP rapidly rises to a peak during the early morning hours, a time when there is also a clear trend toward an increased incidence of adverse cardiac events. Additionally, a relationship appears to exist between various morning triggers that alter the body's hemodynamic forces, and elevations in BP and cardiovascular episodes. Consequently, it is important to ensure optimal BP control in the early morning. Many clinicians remain unaware of the circadian variations in BP and cardiovascular activity and its impact on disease management. The ideal antihypertensive agent should provide smooth, consistent BP control over an entire 24-hour span, with peak plasma drug levels and highest pharmacodynamic effect coinciding with morning elevations in BP. Although a chronotherapeutic approach to hypertension management may offer advantages over conventional therapies, it is clear that long-term clinical studies are needed to explore a variety of issues, including the time of day that drugs are administered, chronological and physiological factors, and individual patient characteristics. While trials examining cardiovascular endpoints are lacking, the use of antihypertensive chronotherapeutic therapies to blunt the surge in early morning BP and control 24-hour BP levels will likely yield positive clinical outcomes. ■

The ideal antihypertensive agent should provide smooth, consistent blood pressure control over an entire 24-hour span, with peak plasma drug levels and highest pharmacodynamic effect coinciding with morning elevations in blood pressure.

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Main Points

- Results of the ambulatory study of the Systolic Hypertension in Europe (SYST-Eur) trial,[23] which compared the prognostic significance of conventional and ambulatory BP measurements, showed that ambulatory systolic BP was a significant predictor of cardiovascular risk in untreated hypertensive patients.
- Morning changes in the sympathetic system result in elevations in blood pressure (BP), heart rate, cardiac output, peripheral resistance, myocardial contractility, and myocardial oxygen demand.
- Studies monitoring the 24-hour BP profiles of normotensive patients have confirmed the characteristic circadian pattern of morning elevations and nighttime reductions in BP, and suggest that the rapid increase in BP during arousal from sleep has an important role in precipitating early morning cardiovascular events.
- Taken together, these data indicate that nighttime administration of chronotherapeutic antihypertensive agents provides efficient lowering of BP during the potentially dangerous morning hours.

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