Circadian Variation in Blood Pressure Implications for the Elderly Patient

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In most people, blood pressure (BP) displays a characteristic diurnal pattern, with a decline during sleep and a sharp increase around the time of awakening. The early morning surge in BP is synchronous with an increase in the risk of catastrophic cardiovascular events, including acute myocardial infarction, sudden cardiac death, and stroke. Although most clinical investigations have centered on modulating or even preventing the morning surge, emerging data suggest that it may be important to avoid nocturnal hypotension, especially in elderly patients and those with established atherosclerotic disease. Considerable evidence has been accumulated to suggest that excessive lowering of BP at night (whether naturally or through the use of antihypertensive medications) can result in untoward ischemic phenomena, including silent cerebral damage (Binswanger’s disease) or ophthalmologic symptoms (eg, anterior ischemic optic neuropathy). Controlled-onset extended-release verapamil, through its unique delivery system, tends to diminish the morning BP surge, whereas it preserves a normal nocturnal BP decline; its effect on preventing early morning cardiovascular catastrophes (while preserving relatively normal nocturnal BP) is currently being tested in a large, international clinical trial. Am J Hypertens 1999; 12:43S–49S © 1999 American Journal of Hypertension, Ltd.

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Although a diurnal variation in blood pressure (BP) and heart rate (HR) has been recognized since 1914, recent reports of circadian variation in cardiovascular ischemic syndromes have suggested that there may be a link between the morning surge in BP and HR, and the increased risk of acute myocardial infarction, stroke, and sudden cardiac death during the early morning hours. Other adverse cardiovascular events that occur more commonly in the early morning hours include cardiac arrest (both in-hospital and out-of-hospital), discharge of automatic implantable defibrillators, symptomatic atrial fibrillation, and ST-segment changes consistent with ischemia (detected by Holter monitoring). Both endogenous and exogenous factors that are more prominent in the morning may promote rupture of atherosclerotic plaque, which then serves as the nidus for coronary or cerebrovascular thrombosis.1

The early morning hours centered around awakening, during which an upright posture is assumed and activities of daily living commence, are associated with a pronounced rise in plasma catecholamine levels. Catecholamines tend to augment coronary vascular tone, decrease vessel caliber, and have positive inotropic and chronotropic effects on the heart. At the same time of day, there is also a rise in plasma cortisol (which enhances vascular sensitivity to catecholamines), an increase in platelet aggregability, and an increase in blood viscosity, which is not offset...
by a countervailing rise in tissue plasminogen activator. These factors, along with the increase in BP and HR, combine to enhance myocardial oxygen demand, diminish myocardial oxygen supply, and promote a hypercoagulable state. These may be the principal physiologic foundations underlying the increase in cardiovascular and cerebrovascular adverse events observed during the morning.

The nocturnal decline in BP has three major consequences that are clinically important. First, the lower the nocturnal BP nadir, the more pronounced the morning surge. Second, there is concern that patients (especially the elderly) who have an extreme nocturnal fall in BP (ie, extreme dippers) have more cerebral ischemia, resulting in the Binswanger’s lesions, cerebrovascular, and periventricular hyperlucencies seen on magnetic resonance imaging of the brain. Third, excessively low nocturnal BP can result in other ischemic phenomena, such as anterior ischemic optic neuropathy (AION).

**NOCTURNAL BP FALL IN THE ELDERLY**

A cooperative ambulatory BP monitoring project involving 4765 normotensive subjects collected by many investigators in several countries has recently defined the normal range for age-specific decline in nocturnal BP. Figure 1, which shows this pattern in both men and women, suggests that the majority of normotensive persons have about a 10% to 20% decline from daytime to nighttime.

Figure 1 also demonstrates that older people have a smaller nocturnal BP fall, whether measured in terms of mm Hg or as a proportion of the daytime BP. Staessen and colleagues also reported that the probability of being a nondipper (ie, exhibiting no BP fall, or even a rise, from daytime to nighttime) increased 2.8-fold from age 30 to 60 years and 5.7-fold from age 60 to 80 years. Proposed explanations for these observations include the facts that older people spend more time in bed than younger people, and they experience less slow-wave sleep, more wakefulness at night, and more fragmentation of sleep than younger individuals. In addition, the elderly experience a larger morning surge in BP than younger people, and, over time, particularly if they have experienced longstanding hypertension, they tend to develop more areas of potential ischemia (watershed areas) in the brain, heart, kidney, and peripheral vasculature. Lastly, older persons have a higher absolute risk of cardiovascular events than younger people, solely due to their age, but perhaps attributable in part to cardiac arrhythmias secondary to sleep apnea, which is more common among people >65 years.

**FIGURE 1.** Nocturnal pressure decrease (top) and night-day ratios (bottom) for systolic (filled symbols) and diastolic (open symbols) blood pressures in 10-year age classes in 3730 normotensive men (left) and 3590 normotensive women (right). Reprinted from Staessen et al: Nocturnal blood pressure fall on ambulatory monitoring in a large international database. Hypertension 1997;29:30–39, with permission.

**EVIDENCE SUPPORTING A POSSIBLE RELATIONSHIP BETWEEN THE MORNING SURGE IN BP AND CARDIOVASCULAR EVENTS**

Two recently reported metaanalyses encompassing many studies and exceedingly large numbers of patients have demonstrated an increased incidence of cardiovascular events in the morning. In one metaanalysis of myocardial infarction and sudden cardiac death, Cohen et al presented findings from a total of 29 studies involving 83,929 patients whose time of onset of myocardial infarctions (MI) had been reported. In those who experienced MI (n = 66,635), there was a 40% increase between 6 AM and 11:59 AM, compared with what would have been expected if the MI had been evenly distributed throughout the 24 h of the day (Figure 2). The metaanalysis also looked at world experience with sudden cardiac deaths. In this cohort of 19,390 patients investigators found a similar 29% increase in risk of cardiac death between 6 AM and 11:59 AM. Recently a metaanalysis of the timing of the onset of acute stroke involving 31 studies and
11,816 patients demonstrated a morning increase in risk of stroke of 49% (compared with the expected result if strokes occurred randomly and evenly throughout the day) (Figure 3).

Each of the foregoing trends may be related to the morning rise in BP. The now-familiar graphs demonstrating the diurnal variation in BP and HR were published in 1978 by Millar-Craig and colleagues and demonstrated, through continuous intraarterial BP recordings in 20 hypertensive and five normotensive ambulatory patients, that BP peaked in the mid-morning hours, then decreased progressively for the rest of the day. Blood pressure was observed to reach its lowest value at 3 AM and increase again by about 20% between 6 AM and 8 AM, around the time of awakening.

Although this landmark work was published two decades ago, only within the last 5 years have there been studies showing its clinical relevance, with a correlation to the morning increase in adverse cardiovascular events. In one of the more intriguing and clearest examples, a Belgian group prospectively determined the time of day calls were received for out-of-hospital cardiac arrests among persons >18 years between 1983 and 1990 in seven cities served by centralized ambulance services. Of 4719 out-of-hospital cardiac arrests 3471 were of presumed cardiac etiology, whereas 1248 were judged to be noncardiac in origin (eg, drowning, suicide). A strong circadian variation, beginning about 6 AM and peaking about 10 AM, was seen in arrests thought to be the result of cardiac disease; this pattern was not seen for ambulance runs for noncardiac conditions.

The Belgian findings showing an increased need for cardiac ambulance transport were corroborated in a study from Houston. Because of the often vast expanses separating sick patients and tertiary hospitals in the large state of Texas, helicopters are often used for expeditious patient transport. The Baylor investigators conducted a prospective study of requests for helicopter transport of 1128 consecutive air-transported patients over a 2-year interval. Data on a total of 787 cardiac and 315 noncardiac patients were collected and the times of requests for helicopter sorties recorded using hourly intervals. A circadian variation was evident in requests for transport of cardiac patients, with a pronounced rise from 6 AM until noon; the noncardiac patients differed significantly (P < .009 by Wilcoxon rank sum test; P < .032 by Kolmogorov-Smirnov test), and showed a more evenly distributed 24-h pattern.

**POTENTIAL DANGERS OF NOCTURNAL HYPOTENSION: SILENT CEREBROVASCULAR DAMAGE**

Because of the high prevalence of atherosclerotic cerebrovascular disease in older patients with hypertension, elderly patients may be more susceptible to either silent (eg, Binswanger’s lesions, lacunae, periventricular hyperlucencies) or symptomatic cerebrovascular damage (eg, transient ischemic attack or stroke) than younger individuals. The first study to address the issue of whether lower nocturnal blood pressures might be troublesome was performed in 100
Japanese patients with sustained hypertension aged >60 years, who had both ambulatory BP monitoring done after at least a month without medications, and a magnetic resonance imaging (MRI) study of the brain. The results of the MRI are shown in Figure 4; among the 16 patients showing a 20% drop in nocturnal BP as compared with daytime readings (extreme dippers), about half had cerebral lacunae and 70% displayed periventricular hyperlucencies. These MRI lesions presumably result from silent cerebral ischemia, and are sometimes known as Binswanger’s lesions, after Otto Binswanger (1852 to 1929), Director of the Psychiatry Clinic and Dean of the Medical School at Jena, who first described similar lesions in autopsied brains. The 46 patients whose nocturnal BP did not change by even 10% compared with daytime (non-dippers) also had an excess prevalence of these abnormalities compared with the 38 normal dippers (with a 10% to 20% dip in nocturnal BP). However, the extreme dippers had far more MRI abnormalities than either of the other groups. The authors suggested that one reason for the greater degree of cerebrovascular damage in extreme dippers may be that, in hypertensive individuals, the lower limit of BP for autoregulation of cerebral perfusion is shifted upward; a pronounced decline in nocturnal BP might cause cerebral ischemia, particularly in vascular beds already affected by atherosclerosis.

The greater susceptibility of elderly people to silent cerebral infarction (SCI) was demonstrated recently by another Japanese team. These investigators matched 60 elderly (age >60 years) and 40 middle-aged (age ≤59 years) hypertensive patients with respect to gender and left ventricular mass index (to account for differences in cardiac end-organ damage); all patients had both ambulatory BP monitoring and an MRI. In all subjects, there was a direct relationship between BP and MRI lesions: higher systolic and diastolic blood pressures were correlated with a greater prevalence of lacunae and SCI (which was more common in the elderly). The most important difference, however, was that, in the elderly (but not in the younger patients), a greater degree of SCI was seen in individuals with the lowest nocturnal blood pressures. The authors therefore concluded that nocturnal hypotension may be the cause of greater SCI in older individuals.

The J-shaped relationship between nocturnal BP decline and silent cerebrovascular disease was confirmed in a recent Japanese study that also assessed sympathetic nervous system activity and HR variability in 51 asymptomatic elderly (aged ≥60 years) hypertensive patients. Multiple lacunae on MRI were noted in 56% of the extreme dippers, 38% of the non-dippers, and only 6% of the normal dippers (P < .01). Similarly, advanced periventricular hyperlucencies were present in 44% of extreme dippers, 22% of non-dippers, and 18% of normal dippers. Extreme dippers also exhibited lower asleep low-frequency/high-frequency ratios, a marker of sympathetic nervous system activity. In contrast, nondippers had lower awake low frequency/high frequency ratios and asleep/awake ratios for high frequency, an index of parasympathetic nervous system activity.

**ADVERSE OPHTHALMIC CONSEQUENCES OF NOCTURNAL ISCHEMIA**

AION has become recognized as one of the most common causes of permanently impaired vision, particularly after the age of 50 years (approximately 6000 cases in the US each year). The pathophysiology of this defect is thought to involve hypoperfusion of the posterior ciliary artery leading to infarction of the optic nerve head, which is recognized as papilledema.

In an epidemiologic study conducted over 20 years at The University of Iowa, which receives these cases imported from all over the state, blurred vision was reported upon arising in 73% of 544 episodes.
Unfortunately, proposed treatments for AION, which include systemic steroids and surgical procedures (eg, optic nerve fenestration), have not proved beneficial in NIH-sponsored clinical trials, so preventive strategies (including aspirin) are of great interest. Consistent with the premise that AION has an ischemic cause, its risk factors include hypertension, diabetes, cigarette smoking, and dyslipidemia.

The initial studies of AION and its possible link to nocturnal hypotension were reported by the group at the University of Iowa, led by Professor Hayreh. The results of ambulatory BP monitoring are shown in Figure 5. As compared with the usual 10% to 20% decline in nocturnal BP compared with daytime readings, 51 patients with AION had substantially greater reductions in nocturnal BP; systolic BP declined 25.3%, and diastolic BP by 31.2%. A possibly more compelling observation was made when the AION patients were divided into two groups: those who suffered continued deterioration in their visual fields, and those whose visual field defects stabilized over time. Patients with continued visual declines had significantly larger decreases in nocturnal BP than those with stable visual fields (\( P < .05 \)). These observations led to the hypothesis that a pronounced nocturnal BP fall might lead to ischemia of the anterior ciliary artery, triggering the onset of AION.

This hypothesis was tested in a cooperative study from both the United States and Switzerland, using somewhat nonstandard ambulatory BP methodology, by comparing the 24-h BP profiles in individuals recently diagnosed with AION and 24 carefully-matched controls (for age, gender, race, diseases, and BP medications). Although the conclusions drawn by the authors of the study point to a major difference between groups in early morning BP (lower BP was seen in the AION patients), there were only two time points (in either systolic or diastolic BP averages during the 24-h period) when the controls had higher BP than the AION patients. This observation is at least consistent with the hypothesis that AION may be related to relative hypotension, especially at night and on arising.

**CIRCADIAN BLOOD PRESSURE VARIATION: IMPLICATIONS FOR TREATMENT**

There are some data that indicate that drug treatment of hypertension can influence the pattern of circadian rhythmicity of BP, but the results may not always be optimal. In an intriguing Italian study of 18 patients with stage 1 hypertension who underwent 24-h ambulatory BP monitoring, the short-acting angiotensin-converting enzyme inhibitor quinapril was administered, after a placebo-treatment period, at a dose of 20 mg/day at either 8 AM or 10 PM in a cross-over fashion. When administered in the morning, quinapril controlled BP well during the daytime, and did not excessively lower nighttime BP, perhaps because of its relatively short serum half-life of 5 h. With 10 PM dosing, however, there was a much larger nighttime drop in systolic BP to 112 to 114 mm Hg between 2 AM and 6 AM (compared with a trough level of 126 mm Hg with morning dosing, and 130 mm Hg with placebo), and an increased surge in BP between 6 AM and 8 AM, presumably due to the lower nocturnal trough. There is concern that this additional 10% to 15% lowering of BP during the night seen with the bedtime administration of quinapril might put patients at risk for the adverse consequences of cerebral ischemia discussed previously.

A delivery system has recently been developed that releases its antihypertensive medication during the
early morning hours and allows very little delivery into the bloodstream during the nighttime. Controlled-onset extended-release (COER) verapamil, taken in the evening, releases its antihypertensive medication in the early morning hours, when it is most needed to control both BP and HR. The unique water-soluble delay coating prevents release of verapamil until 4 to 5 h after ingestion, thereby not disturbing the nighttime trough in both BP and HR. The only delivery of verapamil during the evening and nighttime hours occurs from the previous day’s dose, as the osmotic pump (which is activated by gastrointestinal fluids that enter the tablet only after the water-soluble delay coat has been eroded away) is designed to deliver drug throughout a 24-h period at a constant rate through two precision laser-drilled holes in the plastic shell. The pharmacokinetics of verapamil, delivered by this novel system, were studied in 29 healthy men after 5 days of oral dosing at 10 PM. Plasma levels of R-verapamil, the enantiomer that lowers BP, were quite low during sleep, when exacerbation of the usual nocturnal BP drop could result in untoward ischemic consequences, but then peaked during the early morning hours, synchronous with the diurnal surge in BP, HR, and catastrophic cardiovascular events. Plasma levels of S-verapamil were much lower than the R-antipode, reflecting enhanced first-pass metabolism of the S-enantiomer by the liver. Because S-verapamil is commonly thought to cause more cardiac conduction delays and defects, the reduction of the 1:1 ratio (the racemate found in the COER-verapamil tablet) by hepatic metabolism may be the reason why fewer patients taking this long-acting preparation develop second- and third-degree heart block than the older, immediate-release preparation, which largely avoids first-pass hepatic metabolism.

The morning and nocturnal hemodynamic effects of two antihypertensive regimens that differ markedly in the way the medication is delivered over time were recently compared in 557 hypertensive patients in an international (47 U.S. and 4 Canadian sites), double-blind, randomized, double-dummy, parallel-group study. The nifedipine gastrointestinal therapeutic system (GITS) is designed to provide exactly the same amount of nifedipine every hour of the day (a homeostatic therapy); the comparator was COER-verapamil (a chronotherapeutic strategy). Ambulatory BP monitoring was used to assess the circadian variation of BP after placebo treatment and after 4 weeks at a stable dose of antihypertensive drug therapy. The medications (nifedipine GITS, 30, 60, 90, or 120 mg, given in the morning; or COER-verapamil 180, 240, 360, or 480 mg, dosed at night) were titrated until the office BP was < 140/90 mm Hg. Although changes in daytime BP were essentially equivalent between the two calcium channel blockers (probably because titrations were based on daytime office BP measurements), there was a statistically greater fall in systolic BP during sleep with nifedipine GITS (−11.0 mm Hg), compared with COER-verapamil (−5.8 mm Hg; P < .001). COER-verapamil also elicited a greater fall in morning HR than did nifedipine GITS (−3.8 beats/min v +2.6 beats/min, respectively; P < .001) and in the rate-pressure product (−1437 v −703 beats/min × mm Hg, respectively; P < .001) as well. The authors of this study concluded that verapamil HCl COER-24 has a more favorable early morning hemodynamic profile than nifedipine GITS and a less marked disturbance of nocturnal BP.

A comprehensive quality-of-life assessment was also performed as a follow-up to this study, to compare how patients felt while taking nifedipine GITS and COER-verapamil. Edema and urination were significantly (P < .05) less of a perceived problem with COER-verapamil. In addition, palpitations, swelling, and muscle cramps showed greater improvement with COER-verapamil than with nifedipine GITS. Both treatments improved headache. Constipation, which is frequently observed with verapamil at high doses, was approximately equivalent with both agents, and was generally mild and of short duration, even though roughly 50% of the patients treated with COER-verapamil took >350 mg/day.

In conclusion, there are two aspects of the circadian variation in BP that deserve attention: the temporal association between the morning rise in BP, HR, and catastrophic cardiovascular events, and the potential dangers associated with an excessive lowering in BP during the night. There is epidemiologic evidence that in older patients and those with established cerebrovascular disease, exacerbating nocturnal hypotension may increase ischemia in watershed areas of the central nervous system, and may have adverse clinical consequences. The long-term comparison of COER-verapamil (which was designed to have a maximal impact on the early morning surge in BP and HR, but minimally affect these parameters during the night) with more usual homeostatically based antihypertensive treatments is now underway in the CONVINCE trial; we may know by the year 2002 whether more morning heart attacks, strokes, and deaths can be prevented with this approach to the treatment of hypertension.

REFERENCES


