

Cardiovascular risk and therapeutic intervention for the early morning surge in blood pressure and heart rate

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Abstract

The incidence of most adverse cardiovascular events appears to follow a circadian pattern, reaching its peak in the morning shortly after awakening and arising. The activities of many physiologic parameters, including hemodynamic, hematologic and humoral factors, also fluctuate in a cyclical manner over 24 hours. It has been suggested that, during the post-awakening hours, the phases of these cycles synchronize to create an environment that predisposes to atherosclerotic plaque rupture and thrombosis in susceptible individuals, thereby accounting for the heightened cardiovascular risk at this time of day. Blood pressure (BP) and heart rate are part of this physiologic process that follows a clear circadian rhythm, characterized by a fall during sleep and a sharp

rise upon awakening. This so-called 'morning surge' in BP may act as a trigger for cardiovascular events, including myocardial infarction and stroke. The clinical implication of these observations is that antihypertensive therapy should provide BP control over the entire interval between doses. For agents taken once daily in the morning, the time of trough plasma drug levels (and lowest pharmacodynamic effect) often will coincide with the early morning surge in BP and heart rate. For these reasons, chronotherapeutic formulations of drugs and intrinsically long-acting antihypertensive agents provide the most logical approach for the treatment of hypertensive patients since they provide 24-hour BP control from a single daily dose plus they attenuate the early morning rise in BP (and heart rate in some instances).

Keywords: Chronotherapeutics; Early morning BP surge; Antihypertensive therapy; Circadian rhythms; Calcium antagonists; Angiotensin II receptor blockers; Beta-blockers.

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Circadian variation of BP

The availability of automated, non-invasive, ambulatory BP monitoring (ABPM) devices has allowed BP and heart rate to be measured intermittently over a 24-hour period (typically at intervals of 15–20 minutes). These recordings have demonstrated that, in most individuals, both BP and heart rate follow a definite and reproducible circadian pattern, which tends to be in synchrony with the individual's sleep-activity cycle¹. As a consequence, the normal circadian BP profile is reversed among night-shift workers, such that BP is at its highest during the night and lowest during the daytime.

In the majority of normotensive and hypertensive subjects, BP is maintained at its highest level during the daytime (from about 10 a.m. to 6 p.m.), and then declines to reach a trough value between midnight and 3 a.m. A slow but steady increase in BP is then observed over the early morning hours, and may even begin during rapid eye movement sleep^{1,2}. At approximately 6 a.m., an abrupt and steep acceleration in BP occurs, coincident with arousal and arising from overnight sleep. This morning BP surge from the low night-time levels to higher daytime levels continues for 4–6 hours after awakening^{3,4} and is characterized by an increase in systolic BP of approximately 3 mmHg per hour and in diastolic BP of 2 mmHg per hour¹. In some cases, there may be a slight overshoot in BP, resulting in a peak during the early-to-midmorning hours². The 24-hour BP profile shows little intra-individual variation, even after an intervening period of several weeks, as long as the activities performed on the monitoring days are quite similar⁵.

In general, the circadian pattern of BP among patients with essential hypertension parallels that of their normotensive counterparts, but BP is

elevated throughout the entire 24-hour period⁶, and the amplitude of the rhythm may be altered. Nevertheless, there are exceptions to this rule. Studies employing ABPM have revealed that many elderly patients (aged > 70 years) and African-Americans do not exhibit a normal nocturnal reduction – or 'dip' – in BP^{7,8}. 'Non-dippers' have been defined in the literature as those patients whose nocturnal decline in BP is < 10% of daytime levels while if the reduction in night-time BP is < 10% of daytime pressure, the patients are known as 'dippers'^{9,10}. This classification becomes of clinical relevance, since non-dippers tend to have more severe hypertensive target organ damage than dippers, which may be explained in part by a higher mean 24-hour BP^{11–13}. The reduction in BP from day to night also tends to be blunted among patients with secondary forms of hypertension and various other pathophysiologic conditions^{2,14}.

Factors influencing the circadian pattern of BP

The interaction of numerous physiologic systems and external environmental influences define the cir-

cadian pattern of BP (Table 1)^{7,8,14–22}. Perhaps the most important of these is the sympathetic nervous system (SNS), which regulates BP on a minute-by-minute basis as well as over the long term^{21,23}. Serial measurements of plasma catecholamines over a 24-hour period indicate that fluctuations in norepinephrine and epinephrine levels correlate closely with the circadian pattern of BP²⁴. Other indices of sympathetic activity, such as heart rate, cardiac output, and peripheral resistance, also show marked reductions during sleep which coincide with the fall in BP. The mental and postural changes that accompany arousal and arising from overnight sleep heighten SNS activity, which probably contributes substantially to the sharp rise in BP over the post-awakening hours²⁵.

Another principal determinant of the circadian pattern of BP is the diurnal variation in renin-angiotensin-aldosterone system activity. More than 30 years ago, Gordon et al.²⁶ demonstrated that plasma renin activity gradually decreases during the day, reaching a nadir at 4 p.m., followed by a gradual increase overnight to a peak at 8 a.m. Closer examination of the circadian pattern of plasma renin activity has since demonstrated that

Table 1 – Parameters influencing the normal circadian pattern of BP.

	Adapted from ¹⁴
Demographic characteristics:	Age > 70 years ⁸ African-American ethnicity ⁷
External factors:	Mental/physical activity ¹⁴ Postural changes Smoking ¹⁸ Alcohol ingestion ¹⁷ Sodium ingestion ²⁰ Caffeine ingestion ¹⁶ Medication (e.g. oral contraceptives) ¹⁹
Neuroendocrine systems:	Sympathetic nervous system ²¹ Renin-angiotensin-aldosterone system ¹⁵ Plasma cortisol concentrations ¹⁴ Nitric oxide levels ²²

there are more complex variations over 24 hours rather than a constant protracted transition between peak and trough levels. However, the circadian variation has still been demonstrated to be a trend towards an increase during the morning¹⁵. Levels of angiotensin II apparently follow the same morning increase as plasma renin activity, though the short plasma half-life of angiotensin II makes confirmation more difficult. Plasma levels of aldosterone follow a similar circadian pattern to the plasma renin activity with an increase in levels during the early hours of the morning that peak around the time of awakening¹⁵.

Circadian pattern of cardiovascular events

Cardiovascular events also follow a circadian periodicity, reaching a peak

during the morning hours^{1,27,28}. In most people, this coincides with the post-awakening BP surge described above and changes in other physiologic variables that occur upon arising from sleep.

Myocardial infarction. Muller et al.²⁸ investigated the circadian distribution of acute myocardial infarction using data from 703 patients in the *Multicenter Investigation of Limitation of Infarct Size (MILIS)* study. The time of myocardial infarction was determined from elevations in the myocardial band of the plasma creatine phosphokinase (CPK-MB method). A statistically significant circadian rhythm in the incidence of myocardial infarction was detected ($P < 0.01$), peaking between 6 a.m. and noon (Figure 1). In fact, it was shown that acute myocardial infarction was three times more likely to occur at 9 a.m. than at 11 p.m. An analysis of data from the *Thrombolysis in Myocardial Infarction Phase II*

(*TIMI II*) trial also revealed a higher incidence of myocardial infarction in the morning, with 34% of all events occurring between 6 a.m. and noon²⁹. Numerous other studies support these findings³⁰⁻³³. Interestingly, the administration of beta-blocking agents in the preceding 24 hours may abolish this morning excess of myocardial infarctions^{29,30}.

Myocardial ischemia. Transient ST segment depression detected by ambulatory electrocardiographic (Holter) monitoring has been shown to be diagnostic of myocardial ischemia in patients with coronary artery disease. Use of this technique has also revealed a circadian pattern in myocardial ischemia during normal daily activities³⁴⁻³⁶. As with acute myocardial infarction, most ischemic episodes occurred over the morning period, the largest proportion within 2 hours of awakening; few episodes were detected during the night-time.

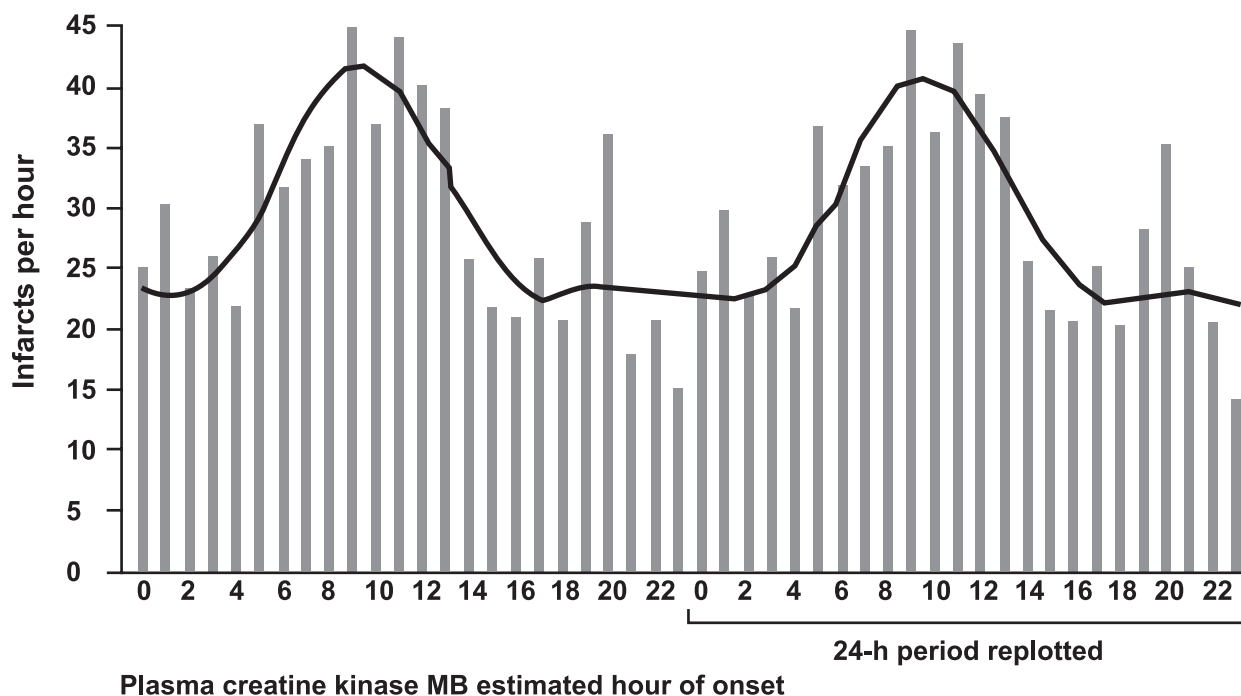


Figure 1 – The hourly frequency of myocardial infarction onset in 703 patients in the *MILIS* database as determined by the CK-MB method (0 represents midnight). The identical data are plotted again on the right to display the relationship between the end and beginning of the day. A prominent circadian rhythm is present with a primary peak incidence of infarction at 9 a.m. and a secondary peak at 8 p.m. Copyright © 1985 Massachusetts Medical Society. All rights reserved²⁸.

This circadian distribution has been confirmed by 24-hour ST segment monitoring of patients admitted to the coronary care unit with unstable coronary syndromes (acute myocardial infarction or unstable angina)³⁷. Significant increases in systolic BP and heart rate were shown to precede a majority (73%) of silent ischemic events detected in a group of men with coronary artery disease³⁸, suggesting that increased myocardial oxygen demand plays a significant role in the genesis of transient ischemia.

Sudden cardiac death. The frequency of sudden cardiac death is also unevenly distributed throughout the day. A careful analysis of mortality data from 5,209 patients in the original Framingham Heart Study database has demonstrated a pronounced and significant ($P < 0.01$) circadian variation in the occurrence of definite or possible sudden cardiac death³⁹. Again, the most vulnerable period was the morning, specifically between 7 a.m. and 9 a.m. when the risk of sudden cardiac death was at least 70% higher than the average risk during other times of the day. A slightly later peak (from 9 a.m. to noon) was reported by Arntz et al.⁴⁰ in a population-based analysis of 24,061 consecutive cases of sudden cardiac death, whereas in the Massachusetts Death Certificate Study, Muller et al.⁴¹ placed the time of highest risk at between 7 a.m. and 11 a.m. Correction of the time of sudden cardiac death according to the time of awakening showed an increased incidence within 3 hours of awakening, suggesting that sudden cardiac death is not simply associated with the time of day, but is a function of the physiologic processes that occur upon arousal from sleep⁴².

Ventricular arrhythmia. The timing of sudden cardiac death is most likely related to the timing of arrhythmias such as ventricular fibrillation and/or tachycardia. Many studies employing

implantable cardiac defibrillators to detect these lethal rhythm disturbances have reported a peak incidence of ventricular arrhythmias (fibrillation, premature ventricular contractions, and tachycardia) between 6 a.m. and noon⁴³⁻⁴⁷. An exception is a study by Wood et al.⁴⁸ in which the majority of ventricular tachyarrhythmias occurred between noon and 5 p.m.

Stroke. There are also numerous studies showing that individuals are most prone to cerebrovascular accidents, including subarachnoid, ischemic and hemorrhagic strokes, and transient ischaemic attacks (TIA), over the morning hours⁴⁹⁻⁵⁷. For example, the temporal pattern of stroke onset was determined from data on the 637 cerebrovascular accidents reported during the Framingham Heart Study⁵². The most common time period for the onset of a stroke was found to be in the morning, with 35% occurring between 8 a.m. and noon. This pattern was maintained when the data were analyzed according to stroke subtype (atherothrombotic brain infarction, cerebral embolism, or subarachnoid hemorrhage), although the peak for intracerebral hemorrhage extended until the mid-afternoon.

Pathophysiologic bases for early morning cardiovascular events

The underlying reasons for the documented excess of cardiovascular events in the morning post-awakening hours have not been fully established. However, several investigations suggest that the physiologic responses related to waking and the beginning of physical and mental activities might trigger these events^{42,58-60}. In addition to BP and heart rate, several other physiologic factors exhibit a marked circadian variation typically linked to the individual's rest-activity pattern,

including catecholamine levels, platelet aggregability, fibrinolytic activity and vascular tone (Figure 2)⁶¹.

Neuroendocrine factors. A number of well-characterized endogenous rhythms may be related to the circadian pattern of cardiovascular events. Plasma catecholamine concentrations have been shown to rise significantly during the morning waking hours⁶², as do plasma renin²⁶ and cortisol levels^{63,64}. The sensitivity of the coronary and systemic vasculature to catecholamine-induced vasoconstriction will be amplified by the concomitant elevation in circulating cortisol. Increased angiotensin II levels resulting from activation of the renin-angiotensin-aldosterone system will also cause peripheral vasoconstriction. Interestingly, it has been shown recently that the normal rise in production of nitric oxide during the morning may be disrupted among patients with hypertension, further potentiating vasoconstriction²². These various neurohormonal patterns provide a plausible explanation for the increased incidence of myocardial ischemia during the post-awakening hours. Catecholamines also exert positive inotropic and chronotropic effects on the heart and may decrease the threshold for arrhythmia.

Hematologic factors. The early morning hours are associated with a heightened tendency for thrombosis. Measurements of platelet activity over a 24-hour period have revealed a sharp increase in platelet aggregability between 6 a.m. and 9 a.m., which are linked to the assumption of an upright posture^{62,65}. Furthermore, the activities of tissue plasminogen activator (tPA) and tissue plasminogen activator inhibitor-1 (PAI-1) – factors that act together to maintain fibrinolytic homeostasis – exhibit inverse circadian patterns. Levels of tPA tend to reach a trough during the morning and a peak in the evening, whereas PAI-1

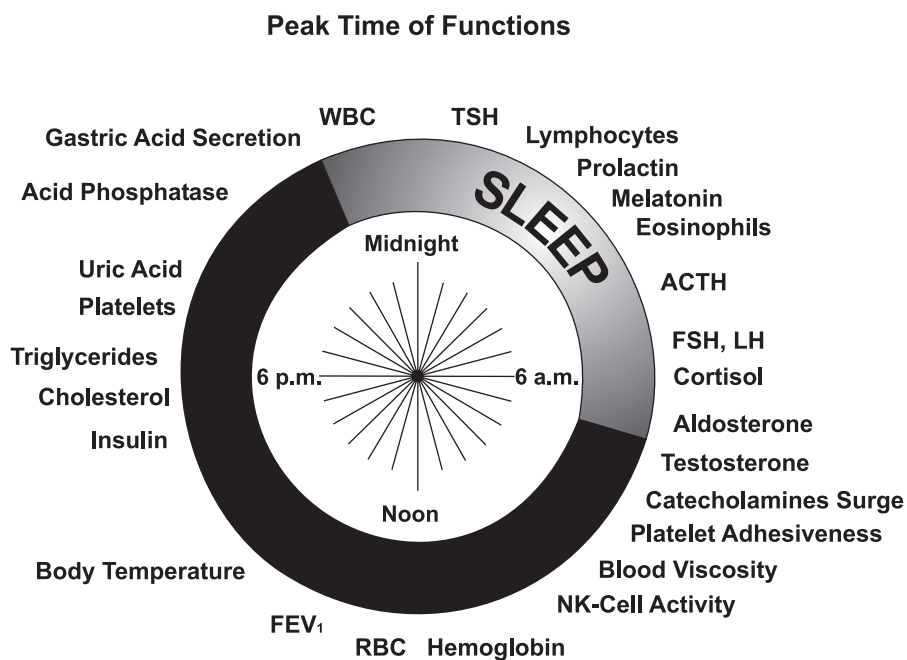


Figure 2 – Peak times of human circadian rhythms for individuals with night-time sleep and daytime activity⁶¹. WBC = white blood cells; TSH = thyroid-stimulating hormone; ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; NK = natural killer; FEV₁ = forced expiratory volume in 1 s; RBC = red blood cells.

displays a reverse pattern⁶⁶. The activity of plasma euglobulin is also reduced during the morning hours, further decreasing morning fibrinolytic activity⁶⁷. Other hematologic factors contributing to the theoretical propensity for thrombus formation in the morning include an increase in blood viscosity⁶⁸ and an elevated hematocrit^{69,70}.

The vulnerable plaque theory. A mechanism based on the interdependency of these various physiologic processes has been proposed to account for the documented high rates of cardiovascular morbidity and mortality in the morning (Figure 3)^{71,72}. While the physiologic responses to awakening are not harmful to normal individuals (in fact, many are necessary), they may have detrimental effects among those with established hypertension or cardiovascular disease.

The central culprit for most cases of myocardial infarction and sudden cardiac death is coronary artery thrombosis⁷³. Pathologic and angiographic studies have indicated that coronary artery thrombus formation most commonly occurs at the site of a ruptured atherosclerotic plaque, although the precise mechanisms leading to plaque rupture have not been fully elucidated. It is, however, reasonable to assume from the morning preponderance of myocardial infarction and sudden cardiac death that the surge in BP and the various vasoconstrictor responses prevalent at this time may promote flow disturbances and dynamic changes in shear stresses, precipitating the rupture of even small vulnerable atherosclerotic lesions. Exposed collagen in the fibrous cap of the plaque may lead directly to the development of an occlusive

thrombus and acute myocardial infarction, sudden cardiac death, or thrombotic stroke. Concomitant increases in blood viscosity and platelet aggregability coupled with a reduction in fibrinolytic activity could produce a hypercoagulable state, further heightening the likelihood that an otherwise harmless mural thrombus overlying a small plaque fissure would propagate and occlude the coronary lumen.

Alternatively, the thrombus may develop gradually, causing reduced blood flow, microemboli and ischemia or even small necrotic foci. Together with the electrical instability resulting from the morning increase in sympathetic nervous system activity, the threshold for ventricular arrhythmias may be decreased, especially among patients with left ventricular hypertrophy (LVH). The imbalance in myocardial oxygen demand and supply produced by the synergistic effects of the humoral vasoconstrictor factors on the coronary arteries together with the sudden acceleration in the rate-pressure product may also lower the threshold for myocardial ischemia^{38,74,75}.

Chronobiological and chronotherapeutic implications for patients with hypertension

General considerations

Cross-sectional data from studies using ambulatory BP monitoring support the importance of 24-hour BP control among patients with hypertension. As already discussed, hypertensive patients maintain a circadian pattern of BP, but values are consistently higher throughout the daytime and night-time compared with normotensive individuals⁶. Consequently it is typically necessary to reduce BP over the entire circadian period. This

concept is further borne out by cross-sectional data from studies utilizing ambulatory BP recordings. The mean 24-hour BP is a better predictor of hypertensive organ damage than an isolated set of office measurements^{2,76,77}. This correlation has been observed both for measures of cardiac target organ damage such as LVH⁷⁸, and for markers of renal microvascular disease such as microalbuminuria⁷⁹. Mancia et al.⁸⁰ have also demonstrated in a longitudinal study that the regression of LVH in patients with hypertension is predicted much more accurately by treatment-induced changes in average 24 hour ambulatory BP than by clinic or even home-monitored BP readings.

Antihypertensive therapy should also provide protection at the time of

greatest risk; that is, the morning post-awakening period when the incidence of acute cardiovascular events reaches a peak⁸¹. Such an approach to disease management is known as ‘chronotherapeutics’, whereby the use of medication is synchronized with circadian physiologic patterns for a favorable patient outcome. Based on this principle, patients with hypertension should be prescribed antihypertensive agents that will provide smooth and consistent BP control over 24 hours, including the vulnerable early morning, post-awakening period. Attenuating or blunting the morning surge in BP could, theoretically, decrease the incidence of acute cardiovascular events that peaks at this time, although conclusive evidence is still lacking.

Chronotherapeutics in cardiovascular disease – the role of beta-adrenergic receptor blockers and calcium antagonists

Various studies have explored the impact of conventional antihypertensive therapy on circadian patterns in cardiovascular events. For example, treatment with the beta-blockers atenolol³⁶ and metoprolol⁸² has been shown to decrease the number of episodes of transient myocardial ischemia that occur during the morning. Some interesting data from the *Intravenous Streptokinase in Acute Myocardial Infarction (ISAM)* study also suggest that beta-blocking agents reduce the morning cardiovascular risk³⁰. Analysis of the timing of acute myocardial infarction in the whole ISAM study population showed a marked increase in incidence between 6 a.m. and noon compared with other times of the day, whereas this morning peak was absent among patients receiving beta-blockers. Similar findings were observed in the MILIS study: a circadian rhythm in myocardial infarction onset was not detected in patients on beta-blockers²⁸. Other reports indicate that beta-blockade also blunts the morning peak in ventricular tachyarrhythmias⁸³, ventricular ectopic beats⁸⁴ and sudden cardiac death⁸⁵. It is likely that these beneficial effects of beta-blockers result from attenuation of the morning surge in sympathetic nervous system activity.

The effects of some of the calcium antagonists on the circadian patterns of cardiovascular parameters have also been recently evaluated. A once-daily, controlled-release formulation of nifedipine – nifedipine gastrointestinal therapeutic system (GITS) – has been reported to attenuate the circadian rhythm of myocardial ischemia in patients with chronic stable angina⁸⁶.

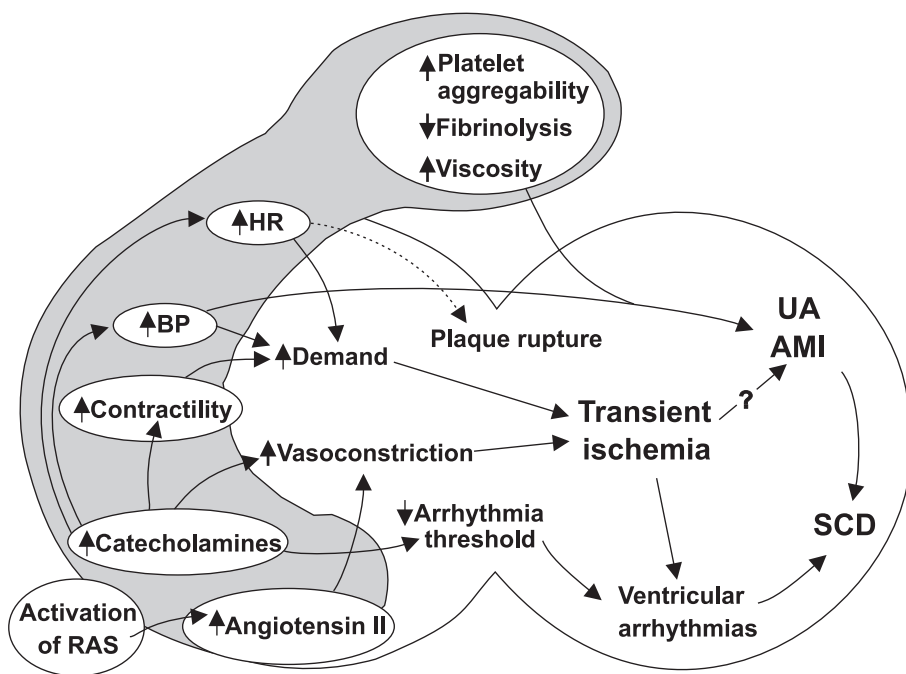


Figure 3 – Possible interrelationships among physiologic processes that occur during the morning waking hours and cardiovascular events in individuals with coronary atherosclerosis⁷¹. AMI = acute myocardial infarction; BP = blood pressure; HR = heart rate; RAS = renin-angiotensin system; SCD = sudden cardiac death; UA = unstable angina.

In contrast, analysis of the ISAM database revealed the persistence of a morning peak in the incidence of myocardial infarction in patients who were receiving calcium antagonists at the time of myocardial infarction³⁰. Although treatment with amlodipine effectively controls the morning BP rise in patients with hypertension⁸⁷, whether or not this translates into a reduced incidence of cardiovascular events at this time of day remains unclear.

The nearly completed *Controlled ONset Verapamil Investigation of Cardiovascular End-points (CONVINCE)* study will assess whether the incidence of fatal or nonfatal myocardial infarction and stroke, and cardiovascular disease-related death is reduced among patients on controlled-onset extended-release (COER) verapamil compared with those on a standard regimen of hydrochlorothiazide or atenolol⁸⁸. In a prior study of over 500 patients with hypertension, COER-verapamil, when administered at bedtime, lowered heart rate, the rate-pressure product (Figure 4), and the rate of rise of heart rate and BP over the morning post-awakening hours more effectively than nifedipine GITS⁸⁹. Both treatments produced similar reductions in early morning and 24-hour ambulatory BP.

Antihypertensive drugs that are administered once daily have become increasingly popular in an attempt to encourage compliance to treatment and minimize recurrent fluctuations in BP that may occur with agents that are taken several times per day^{90,91}. Once-daily drugs can be administered in the morning or evening, but it is possible that taking large doses of antihypertensive medication in the evening might cause nocturnal hypotension (1, 4). In certain susceptible patients (e.g. the elderly, and those with established coronary artery disease, left ventricular dysfunction, or a previous cerebrovascular event),

excessive reduction of BP during the night-time may predispose to silent myocardial ischemia, optic nerve damage and stroke⁹²⁻⁹⁶. Gastrointestinal activity also appears to follow a circadian pattern, with absorption at night being lower than during the day. So, to achieve similar drug levels at night, a larger dose may have to be given, which may, in turn, increase the incidence of side-effects. Thus, for a number of drugs for the treatment of hypertension, morning dosing may be more appropriate than evening dosing.

One potential consequence of once-daily morning dosing is that the peak incidence of cardiovascular events and the early morning surge in BP coincides with the time of the trough level of a particular agent and its lowest pharmacologic effect. Additionally, because patients do not take their medication until they have arisen, BP control during the vulnerable post-

awakening period is dependent on the persistence of pharmacodynamic activity of the dose taken the previous morning. Thus, it is of critical importance that once-daily antihypertensive agent should be effective over the entire 24-hour period between doses.

Studies utilizing ABPM have shown that achieving adequate BP control during the morning is frequently difficult. Some once-daily antihypertensive drugs do not have complete 24-hour BP control as they lose efficacy during the last 4-6 hours of the dosing interval⁶. This may provide one potential explanation for the relative shortfall of antihypertensive treatment in reducing the cardiovascular risk in patients with hypertension: failure to control the early morning BP surge leaves patients susceptible to the various cardiovascular events that occur at this time.

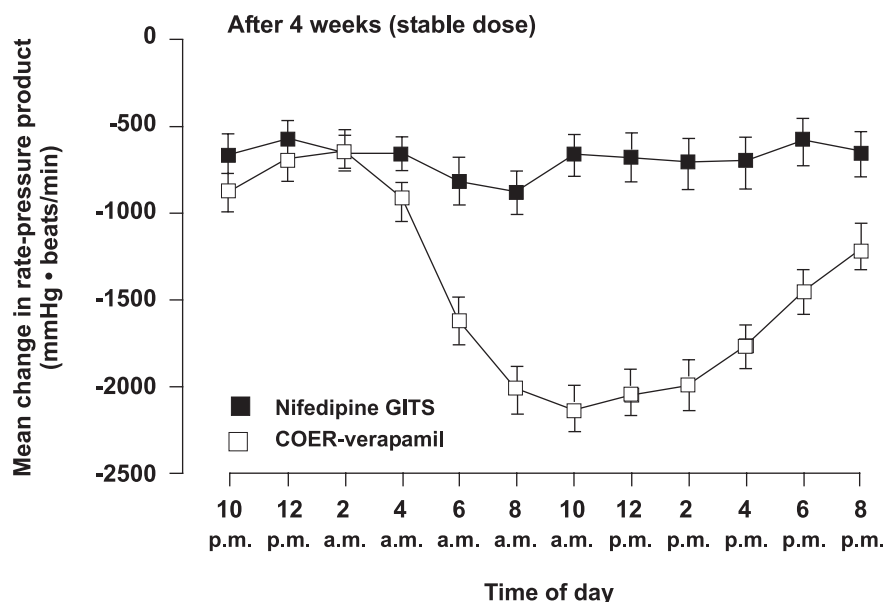


Figure 4 – Changes from baseline in 24-h rate-pressure product after administration of nifedipine gastrointestinal therapeutic system (GITS) given in the morning or COER-verapamil given at bedtime. The study was performed after 4 weeks of stable therapy. Error bars represent 1 SEM change⁸⁹.

Angiotensin II receptor blockers in chronotherapeutics

The angiotensin II antagonists now registered for the treatment of hypertension are all dosed once-daily and lower BP by binding to the angiotensin II subtype 1 receptor in vascular and cardiac tissue. However, ambulatory BP monitoring studies have shown that differences exist among these agents with regard to their duration of action, with the antihypertensive activity of some of these agents declining substantially towards the end of the 24-hour dosing period.

For example, in a randomized, double-blind, multinational, placebo-controlled trial that compared the efficacy and safety of the long-acting angiotensin II receptor blocker telmisartan versus losartan, significant differences were observed during the early morning period⁹⁷. After 6 weeks

of therapy, all active treatments produced significant reductions from baseline in mean 24-hour ambulatory SBP and DBP compared with placebo ($P < 0.05$; Figure 5). However, both doses of telmisartan were significantly more effective than losartan at decreasing ambulatory SBP and DBP over all monitoring periods (the daytime, morning, night-time, and in particular the 18 to 24-hour period after dosing from the previous morning) ($P < 0.05$; Figure 5). In fact, the mean change from baseline in diastolic BP 18-24 hours after drug administration with losartan 50 mg was not statistically greater than with placebo (-3.7 mmHg versus -1.3 mmHg, respectively). In contrast, telmisartan reduced the last 6-hour ambulatory BP means by 10.7/6.8 mmHg and 12.2/7.1 mmHg, for the 40 and 80 mg doses, respectively ($P < 0.05$ versus losartan and placebo for both the systolic and diastolic BP).

Another interesting study by La-courciere et al.⁹⁸ evaluated the duration of action of the long-acting angiotensin II receptor blocker telmisartan versus an equally long-acting calcium antagonist amlodipine in 232 patients with stage I and II hypertension. The efficacy of amlodipine over 24 hours is well documented⁹⁹⁻¹⁰¹. After 12 weeks of treatment, telmisartan produced significantly greater reductions in the night-time and trough (last 4 hours of the dosing interval) diastolic BP than amlodipine ($P < 0.05$; Figure 6). Furthermore, patients on telmisartan had significantly lower ambulatory heart rates than in those on amlodipine during the last 4 hours of the dosing period and between 6 a.m. and noon ($P \leq 0.005$), a finding that may have an important impact on the heart rate-systolic blood pressure product in the early morning.

Multiple factors are behind these findings on circadian BP by the angiotensin II receptor blocker. One factor

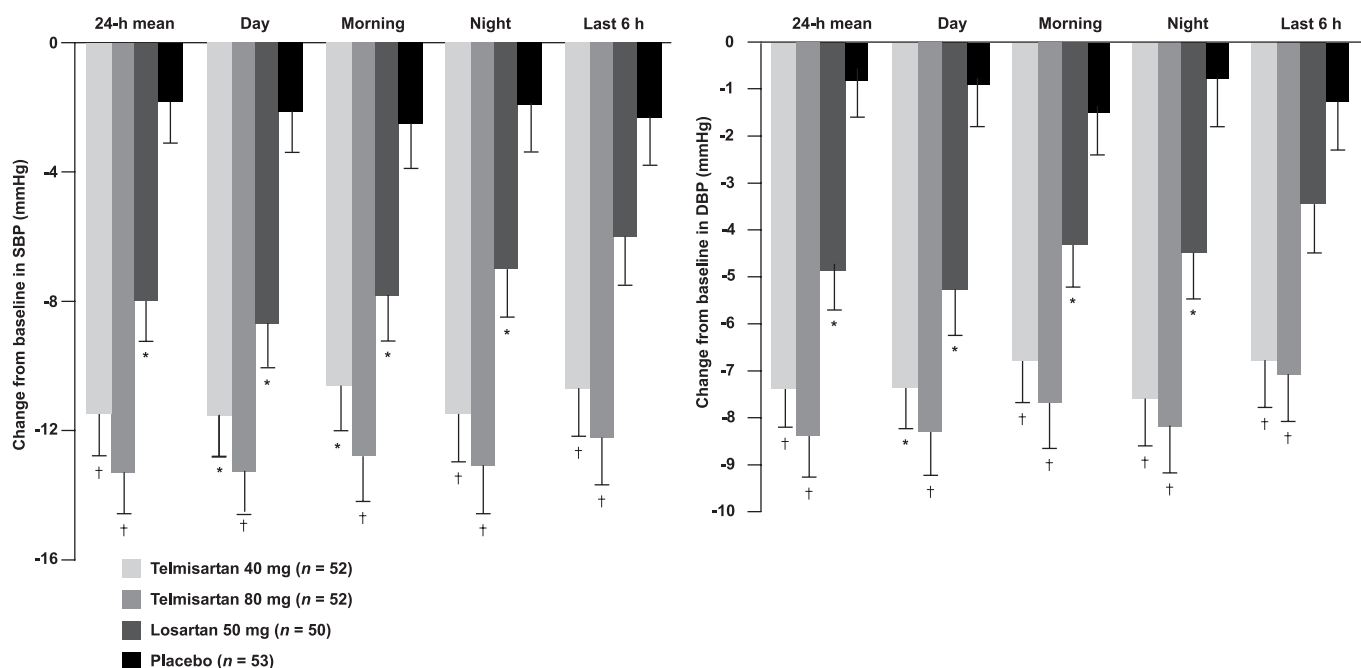


Figure 5 – Mean changes from baseline in ambulatory systolic BP (SBP) and diastolic BP (DBP) after 6 weeks of treatment with telmisartan 40 mg, telmisartan 80 mg, losartan 50 mg or placebo once daily. Mean changes are shown for the entire 24-h period, daytime (6 a.m. to 10 p.m.), morning (6 a.m. to noon), night-time (10 p.m. to 6 a.m.) and the last 6 h of the dosing interval. * $P < 0.05$ compared with placebo; † $P < 0.05$ compared with losartan and placebo⁹⁷.

is the nature of binding between the angiotensin II antagonist and the AT₁ receptor. In the case of telmisartan, candesartan, valsartan, and irbesartan, the binding is described as insurmountable (or non-competitive), thus the drug binds tightly to the AT₁ receptor and is released slowly with a low drug-receptor dissociation constant¹⁰². In addition, telmisartan is a highly lipophilic agent ($\log P$ [n-octanol/buffer] +3.2), which may also contribute to its duration of action. A highly lipophilic compound will readily permeate the plasma membrane and, once inside the cell, bind reversibly to proteins. This protein-bound drug serves as a reservoir, allowing the gradual release

of the compound over an extended period. Because telmisartan has a high volume of distribution (7 L/kg)¹⁰³, it will disperse readily into the tissue compartment, thereby increasing the size of the intracellular protein-bound reservoir.

Conclusions

A variety of biologic functions, such as BP, heart rate, sympathetic nervous system activity, vascular tone, platelet aggregability and fibrinolysis exhibit a circadian rhythm and may contribute to the morning peak of cardiovascular events. Based on the principles of

chronobiology, it would be logical to assume that antihypertensive therapy should provide protection during this period of increased cardiovascular vulnerability. In addition to the obvious impact of the catecholamine hormones directly, the importance of the generation of renin, angiotensin II, and aldosterone in the early morning period and its contribution to the early morning surge in BP has evolved in the literature. Data from ambulatory BP trials suggest great potential for protection against the angiotensin II-mediated physiologic responses to awakening that might contribute to the excess of cardiovascular events observed around this time.

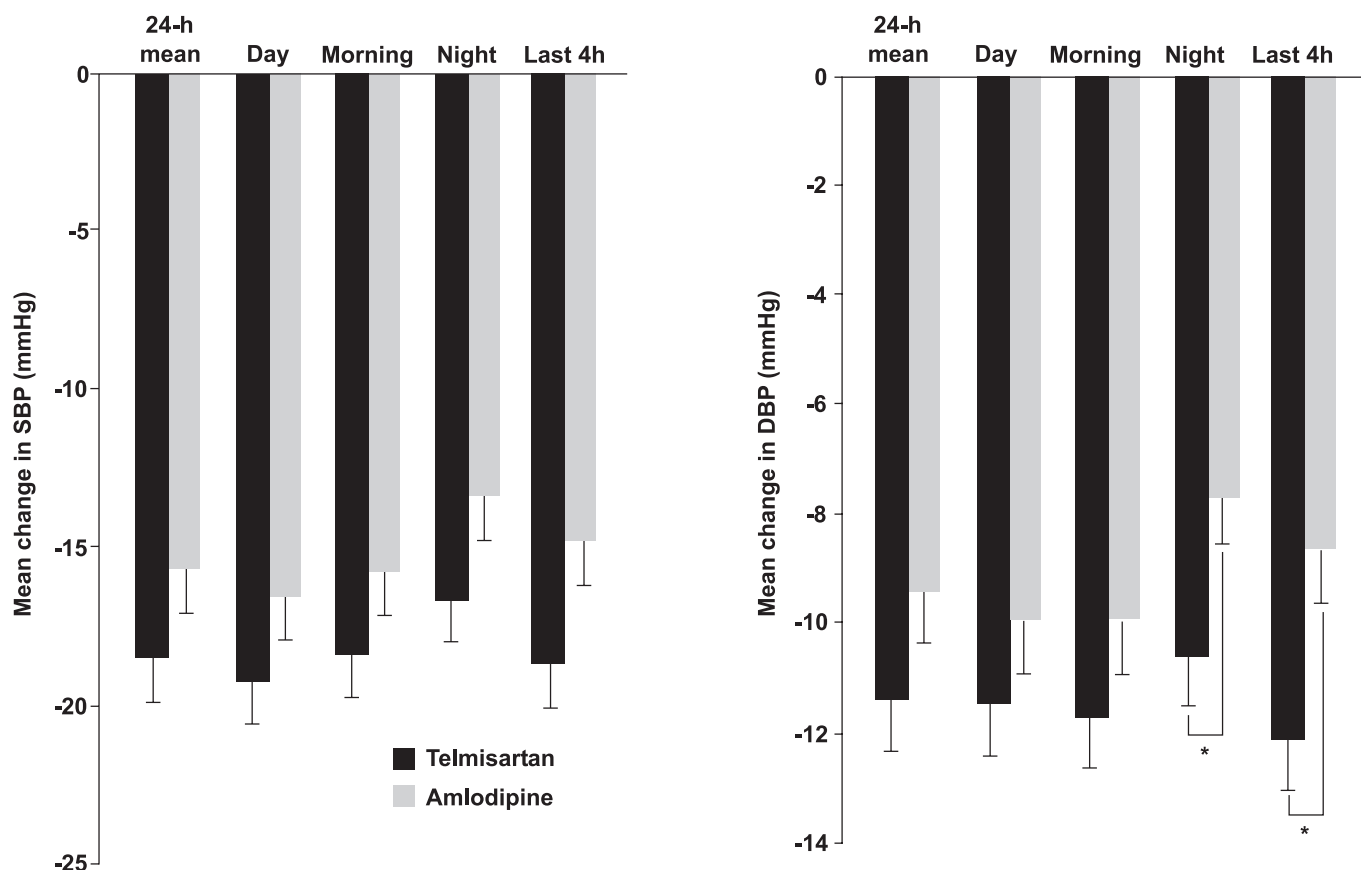


Figure 6 – Mean changes (\pm SEM) from baseline in 24-h ambulatory systolic (SBP) and diastolic BP (DBP) after 12 weeks of treatment with telmisartan 40-120mg or amlodipine 5-10 mg once daily. Mean changes are shown for the entire 24-h period, daytime (6 a.m. to 10 p.m.), morning (6 a.m. to noon), night-time (10 p.m. to 6 a.m.) and the last 4 h of the dosing interval⁹⁸. * $P < 0.05$ for telmisartan compared with amlodipine.

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