Inability to supply oxygen to the myocardium when demand is high appears to be related to several cardiovascular events, including transient myocardial ischemia, acute myocardial infarction, and sudden death. Myocardial oxygen consumption is correlated with the rate-pressure product (heart rate \( \times \) systolic blood pressure) and this hemodynamic parameter has been shown to follow a circadian pattern similar to that observed with cardiovascular events. However, the clinical implications of this observation and the appropriate clinical interventions have not been studied. Therefore, the impact of the chronotherapeutic controlled-onset extended release delivery (COER-verapamil) on heart rate and the rate-pressure product was assessed and compared with that of nifedipine gastrointestinal therapeutic system (GITS), which is designed to provide a constant or homeostatic drug effect. A total of 557 hypertensive patients were enrolled in the 51-center, randomized, double-blind prospective study. Twenty-four–hour ambulatory blood pressure (BP) monitoring was performed at baseline, after 4 weeks of stable-dose therapy, and after 10 weeks of treatment; heart rate was assessed concomitantly. Heart rate, rate of rise (slope) of BP and heart rate, and the rate-pressure product were all reduced to a greater extent by COER-verapamil during the early morning hours compared with the nifedipine GITS treatment. Thus, COER-verapamil exerted a beneficial hemodynamic profile for the treatment of the increases in rate-pressure product typically observed in the early morning in patients with hypertension. Am J Hypertens 1999;12:50S–55S © 1999 American Journal of Hypertension, Ltd.

**KEY WORDS:** Heart rate, systolic blood pressure, rate-pressure product, chronotherapy, controlled-onset extended release delivery system.

The incidence of transient myocardial ischemia, myocardial infarction (MI), nonfatal MI, and sudden death follows a circadian pattern, with peak time for onset during the first hour before and the 3 h after awakening.\(^1\)--\(^3\) Heart rate and systolic blood pressure (BP) follow a similar pattern, rising sharply between 6 and 9 AM.\(^4\) Further, these two hemodynamic parameters have been shown to increase significantly 1 min before the onset of silent ischemic events.\(^5\)

Epidemiologic data have also demonstrated a positive relationship between elevated resting heart rate and increased mortality.\(^6\),\(^7\) In the Göteborg Primary Prevention Trial, investigators discovered that total mortality increased with rising resting heart rate, peaking when heart rate was 90 to 99 beats/min.\(^6\) Data derived from a 26-year follow-up of men aged 35 to 84 years during the Framingham Study showed that men in the highest two quintiles of resting heart rate (80 to 87 and \( \geq 88 \) beats/min, respectively) were at signifi-
cantly increased risk for cardiovascular mortality in general and sudden death in particular. In a recent metaanalysis of several relevant studies, Palatini and Julius confirmed this association and also noted that individuals with elevated heart rates were more likely to develop hypertension than subjects with low rates.

Myocardial oxygen consumption is the most important indicator of the load on the heart. Major determinants of myocardial oxygen demand are left ventricular systolic pressure, radius, and mass, contractility, and heart rate. Although myocardial oxygen consumption is difficult to measure directly, the rate-pressure product (heart rate \(\times\) systolic BP) is a strong correlate of myocardial oxygen consumption and is an easy parameter to measure in ambulatory patients.

In both normotensive and hypertensive men with coronary artery disease, the occurrence of ischemic events in the early morning period has been shown to be closely related to increases in the rate-pressure product. Further, many of these events were preceded by a nearly 20% increase in the rate-pressure product approximately 5 min before onset of ST-segment depression (Figure 1). These findings, in addition to the recognized circadian variation in cardiovascular events, suggest a role for a chronotherapeutic approach to treating hypertension and ischemic heart disease. Timing of a drug’s effects to align with the intrinsic circadian variation of the illness may prevent cardiovascular events.

**EVALUATING EFFECTS OF CHRONOTHERAPY ON HEART RATE AND RATE-PRESSURE PRODUCT**

A recent study assessed the impact of chronotherapy on BP, heart rate, and rate-pressure product, particularly during the early morning hours, in patients with hypertension. The study compared the effects of a controlled-onset extended release delivery system (COER-verapamil) with those of a homeostatic delivery system (nifedipine gastrointestinal therapeutic system [GITS]), which is designed to provide a constant drug effect.

A total of 557 patients were randomized to receive either COER-verapamil \((n = 276)\) or nifedipine GITS \((n = 281)\). Patients were titrated for 180 mg to 480 mg every night for verapamil and 30 to 120 mg every morning for nifedipine based on office BP measurements \((<140/90 \text{ mm Hg})\). Among the patients who received drug treatment, 400 achieved normotensive office BP during the study \((n = 202 \text{ for COER-verapamil and } n = 189 \text{ for nifedipine GITS})\), although many patients required an intermediate or high dose to do so.

The primary variable for assessing efficacy was the change in early morning BP (the 4-h period defined as 1 h before to 3 h after awakening) from baseline after 4 weeks of taking a stable dose of COER-verapamil or nifedipine GITS. The two treatments were defined as clinically equivalent if the mean change from baseline between groups in early morning systolic BP was \(\leq 5 \text{ mm Hg} \text{ and } \leq 3 \text{ mm Hg}\) for diastolic BP. Other study efficacy measures included changes from baseline in the early morning \(1 \text{ h before and } 3 \text{ h after awakening}\), changes in heart rate, rate-pressure product, and the rate of rise (slope) of BP and heart rate. Additionally, changes from baseline in 24-h mean, awake, and sleep BP and heart rate were compared for the two treatment groups. Actual awake and sleep times have been determined to be preferable to arbitrary daytime and nighttime averages of ambulatory
BP and heart rate, as they result in more accurate assessments of sleep BP, in particular. At 4 weeks after stabilization of drug dosing and at the end of 10 weeks of therapy, mean changes in early morning BP were clinically equivalent between the two treatment groups. The patients receiving nifedipine GITS did experience a clinically significantly greater reduction of nocturnal systolic BP (5.2 mm Hg greater among patients receiving the homeostatic therapy versus COER-verapamil; \( P < .001 \)).

Changes in early morning heart rate from baseline differed significantly between the two groups (\( P < .001 \)). In patients who received nifedipine GITS, heart rate increased approximately 2 beats/min, compared with a decrease of about 4 beats/min in the COER-verapamil patients (Figure 2). The mean changes in heart rate during awake periods versus sleep reflected a similar trend. Heart rate was increased among nifedipine GITS patients during the awake period, whereas it decreased significantly among those receiving COER-verapamil (\( P \leq .001 \) between treatment groups) (Figure 3).

Both drugs decreased the rate of rise in BP at 4 and 10 weeks of treatment. However, the rate of rise in heart rate during the early morning period was increased with nifedipine GITS treatment and was decreased significantly with COER-verapamil therapy (\( P < .001 \)).

COER-verapamil exerted a significant effect on the rate-pressure product, especially in the early morning. At 4 weeks, the mean changes in rate-pressure product during the early morning period were \(-703 \pm 1568\) mm Hg beats/min and \(-1437 \pm 1864\) mm Hg beats/min in the COER-verapamil and nifedipine GITS groups, respectively (\( P < .0001 \)). At the end of the study, COER-verapamil continued to demonstrate this effect, significantly more so than nifedipine GITS (\(-1490 \pm 1879\) mm Hg beats/min versus \(-917 \pm 1638\) mm Hg beats/min, respectively, \( P = .0003 \)).

For all ambulatory monitoring parameters, COER-verapamil demonstrated a greater slowing effect on heart rate than nifedipine GITS. The difference between the two groups was highest during the awake period at 4 and 10 weeks of therapy (8 and 9 beats/min, respectively). During sleep, this difference was not as great (4 and 3 beats/min at 4 and 10 weeks of therapy, respectively).

Mean reductions in 24-h ambulatory rate-pressure product at 4 weeks of stable dosing were greater among patients in the COER-verapamil group than in those in the nifedipine GITS group, predominantly over the 12-h period from 6 AM to 6 PM (Figure 4). The most marked effect occurred between 6 AM and 6 PM and was least evident between 10 PM and 4 AM. The average reduction in the rate-pressure product obtained with COER-verapamil treatment approximated...
5% during sleep and was about 20% during the early morning period. In contrast, nifedipine GITS reduced the rate-pressure product about 5% to 7% throughout the dosing interval.

Of the 281 patients in the nifedipine GITS group, 207 (74%) reported at least one adverse event during the study, compared with 188 (68%) among those in the COER-verapamil group (22% v 4%) ($P = 0.05$). The nifedipine GITS group had significantly more peripheral edema than the COER-verapamil group ($P < 0.001$). However, the COER-verapamil group experienced more constipation (15% v 8%) ($P = 0.016$). In a follow-up substudy, data from a 71-symptom checklist that patients completed showed that patients receiving COER-verapamil reported significantly less distress ($P < 0.05$) than those who received nifedipine GITS.13 These findings may have implications regarding patient adherence to long-term therapy.

**CLINICAL IMPLICATIONS**

The primary differences between the two treatment groups were the effects on heart rate and rate-pressure product. COER-verapamil reduced both these hemodynamic parameters during the early morning hours when heart rate and BP typically rise and when the incidence of cardiovascular events peaks (Figure 5).1– 4,8 These statistically significant reductions are clinically important, because several studies have shown that cardiovascular morbidity and mortality increase with increasing heart rate.8,14 It follows that a calcium antagonist that lowers heart rate may provide advantages to patients at risk for cardiovascular complications.

Although the pathophysiology and pathogenesis of myocardial ischemia have not been fully elucidated, decreased myocardial oxygen supply concurrent with increased oxygen demand appears to be an important trigger, especially in the early morning hours. In a study conducted in 50 patients with coronary artery disease and exercise-induced ST-segment depression, ambulatory electrocardiogram monitoring for ST-segment shift during normal activities revealed that most episodes of ischemia correlated with significant in-
creases in heart rate. The patients who experienced ischemia during daily activities underwent stress testing, which demonstrated earlier onset of ST-segment depression occurring at a lower heart rate and rate-pressure product than those without ischemia. Interestingly, ST-segment depression occurred in patients who had a relatively high ischemic threshold during exercise (when heart rate was high).

Deedwania and Nelson provided insight regarding the relation between rate-pressure product and silent ischemia by performing simultaneous ambulatory BP and Holter monitoring in men with silent coronary artery disease. The authors found that a majority of the ischemic events in their study (85 of 92) were silent and followed a circadian pattern. Nearly two-thirds of these events (61%) were preceded by an increase in heart rate of at least 5 beats/min (P < .001). Systolic BP increased an average of 10 mm Hg within 6 min before ST-segment depression in 73% of the silent ischemic events (P < .001). Thus, the statistically significant rise in both heart rate and systolic BP indicates that myocardial oxygen demand, represented by the rate-pressure product, may play a role in the development of silent myocardial ischemia.

In the current study, the reductions in heart rate and rate-pressure product appear to be associated with the release of COER-verapamil and its onset of activity, which is delayed for several hours after bedtime dosing. Drug serum concentrations peak concurrently with peak incidence of cardiovascular events, and then wane during the day until bedtime, when another dose is taken. The modest but steady reduction in rate-pressure product in patients receiving nifedipine GITS is reflective of the homeostatic delivery system, which provides a constant drug concentration.

Although the direct role of heart rate and BP in the pathogenesis of myocardial ischemia remains unknown, it is recognized that a rapid change in heart rate and BP during the early morning hours may trigger myocardial ischemia or infarction. Both COER-verapamil and nifedipine GITS decreased the rate of rise (slope) of BP. However, COER-verapamil significantly decreased the rate of rise of heart rate compared with nifedipine GITS. This finding appears to be dose-related.

Nifedipine GITS induced an 11-mm Hg reduction in systolic BP during sleep, whereas the decrease obtained with COER-verapamil was 6 mm Hg. This, in fact, may not be a benefit of nifedipine GITS therapy. Some authors have suggested that excessive reduction in systolic BP, especially in elderly patients, may lead to induction of cerebrovascular events. Thus, COER-verapamil may be safer because it provides a more constant, intermediate level of systolic BP.

Epidemiologic studies indicate the importance of heart rate in the genesis of cardiovascular events. The circadian pattern of hemodynamic parameters including heart rate and rate-pressure product demonstrate a potentially important role in predicting cardiovascular risk. To test the hypothesis that chronotherapy may reduce the risk for cardiovascular events, a large interventional multicenter study (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints [CONVINCE]) is currently under way to assess the effects of chronotherapy on specific cardiovascular endpoints, as well as circadian variations of morbid events, mortality, and possible triggers of these events.

REFERENCES


