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Chronotherapeutics for Cardiovascular Disease

Yusra Anis Anwar and *William B. White*

Section of Hypertension and Clinical Pharmacology, Department of Medicine,
University of Connecticut School of Medicine, Farmington, Connecticut, USA

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Summary

Chronotherapeutics, or delivery of a medication in concentrations that vary according to physiological need at different times during the dosage period, is a relatively new practice in clinical medicine. Epidemiological studies document that the incidence of many cardiovascular diseases, including myocardial infarction and stroke, varies predictably in time over 24 hours (the circadian period). Advanced diagnostic technologies using ambulatory monitoring of the blood pressure and electrocardiogram have also demonstrated that there is marked variability in the level of pressure in hypertensive patients and the degree of myocardial ischaemia in patients with coronary disease. These diagnostic techniques also allow us to study the effects of varying the timing of administration or delivery of a concentration of a drug on end-points such as changes in blood pressure, heart rate or intensity of angina.

The first chronotherapeutic agent for hypertension and angina pectoris, controlled onset, extended release (COER-24) verapamil, has recently been developed and registered in the US, Brazil, Canada and Mexico. The theoretical advantage of this formulation is that delivery of the active drug, verapamil, has been tailored to the typical circadian rhythm of blood pressure and heart rate in patients with hypertension and angina to better cover the early morning hours when cardiovascular need appears to be the greatest. An outcome study (CONVINCE) that evaluates primary prevention of cardiovascular events with this chronotherapy versus standard of care therapy is under way in several countries in North and South America and Europe.

1. Circadian Variation of Disease

Through a number of clinical trials and epidemiological studies, it has become evident that the levels of disease activity of a number of clinical disorders have a pattern associated with the body's inherent clock set according to circadian (day-night or awake-sleep cycles of 24 hours), monthly or seasonal rhythms.[1,2] The circadian body rhythms are of particular relevance to cardiovascular medicine, including hypertension,[3,4] myocardial infarction[5] and stroke.[6] There are now substantial data that strongly suggest that a number of haemodynamic, environmental and haematological 'triggers' of myocardial infarction and stroke enhance the incidence of these diseases in the early morning hours associated with awakening.

Practising physicians are by and large unfamiliar with the field of chronobiology – the science concerned with the biological mechanisms of the body according to a time structure; chronopathology – the study of the variability of disease processes according to the time of day; and chronotherapeutics – the discipline concerned with the pharmacological delivery of drugs according to inherent activities of a disease over a certain period of time.

Table I. Circadian rhythms and the severity or manifestation of clinical disease. These timings/symptoms are true of those individuals who follow a daytime activity and night-time sleep lifestyle

Disease or syndrome	Circadian rhythmicity
Allergic rhinitis	Worse in early morning/upon arising
Bronchial asthma	Exacerbations more common during the sleep period
Arthritis, rheumatoid	Symptoms are most intense upon awakening
Osteoarthritis	Symptoms worse in the middle/latter portion of the day
Angina pectoris	Chest pain and ECG changes more common during the early morning
Myocardial infarction	Incidence greatest in the early morning
Peptic ulcer disease	Symptoms worse after gastric emptying and in the early (sleep) morning
Stroke	Incidence greatest in the early morning

Abbreviation: ECG = electrocardiographic.

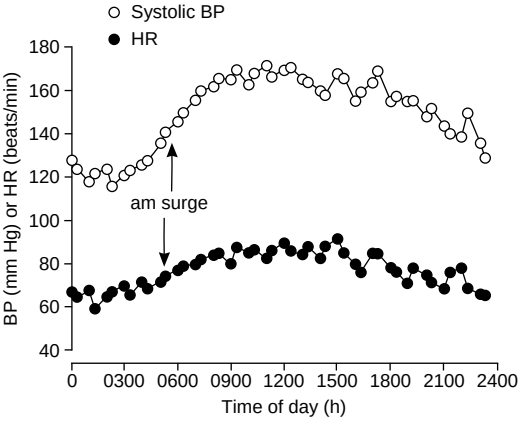

Fig. 1. Typical pattern of systolic blood pressure (BP) and heart rate (HR) from a 24-hour ambulatory monitoring study. The low span during sleep is typically followed by the morning (am) surge where the rates of rise of BP and HR are steep in association with awakening.

This article focuses on the chronobiology of cardiovascular diseases, the methods of analysing drugs according to chronobiological principles and the new potential therapeutic interventions that have been developed in response to the perceived needs for treatment according to known variabilities of the disorders, rather than the standard homeostatic approach to therapeutics.

Humans vary greatly in their biochemical and physiological status over a 24-hour period, due to the staging of a number of circadian rhythms. The rhythmic alterations in our clinical or functional status may cause daytime or night-time differences in the susceptibility and resistance of individuals to either the expression of disease or the intensity of a symptom. As noted in table I, there are a number of common diseases that have been shown to vary their intensities in a cyclical fashion over 24 hours due to chronobiological factors.

In addition to the diseases listed in table I, there are also predictable alterations in disease status and human biological behaviour that occur over other time spans such as the week, the month and the season.[2] However, these areas of chronobiology are outside the scope of this article.

2. Circadian Variation of Blood Pressure and Heart Rate

In both normotensive and hypertensive individuals, blood pressure (BP) varies according to both mental and physical activity levels, especially during wakefulness and sleep. As shown in the example in figure 1, BP and heart rate (HR) are at their highest levels during the period when a hypertensive patient is awake and active (e.g. work) and at their lowest levels during sleep.

In most hypertensive patients, there is a fairly marked rise in BP upon awakening that is called the morning or 'am' surge.[7,8] At this time, the rate of rise of systolic BP is approximately 3mm Hg/hour for the first 4 to 6 hours after awakening, while the figure for the rise of diastolic BP is approximately 2mm Hg/hour.[8] HR typically follows the same pattern as BP; thus, the 'rate-pressure' double-product, a correlate of myocardial oxygen consumption, is accelerating at this time of day.

In most patients with essential hypertension who are diurnally active and nocturnally asleep, the BP generally declines from mid-afternoon on (especially if an individual is employed outside of the home) and reaches its nadir between midnight and 0300h. This 24-hour cycle of BP then repeats itself and is typically quite reproducible in an individual as long as the activity levels for the 2 days are similar.[9]

There have been a number of studies over the past 10 years that have evaluated the relationships between the clinic (or office) BP and the out-of-office or ambulatory pressure. To provide clinical researchers and practising physicians with a frame of reference, an expert committee from the American Society of Hypertension published a document[10] that included 'suggested' upper limits of normal for ambulatory BP (table II). These values, which link the level of ambulatory BP with target organ disease, are based on the research literature as well as the expertise of the panel members of the Society.

Table II. Suggested upper limits of normal for ambulatory blood pressure (BP) [from Pickering et al.,[10] with permission]

Blood pressure measurement (mm Hg)	Probably normal	Borderline	Probably abnormal
Systolic BP			
Awake	<135	135-140	>140
Asleep	<120	120-135	>125
24h mean	<130	130-135	>135
Diastolic BP			
Awake	<85	85-90	>90
Asleep	<75	75-80	>80
24h mean	<80	80-85	>85

Table III. Clinical aetiologies of the loss of nocturnal decline in blood pressure in patients with hypertension

Autonomic dysfunction syndromes
Diabetes mellitus (with neuropathy and/or nephropathy)
Renal insufficiency with volume-dependent hypertension (e.g. dialysis population)
Phaeochromocytoma
Cushing's syndrome
Primary hyperaldosteronism[a]
Drugs (e.g. cyclosporin and high dose corticosteroids)
Severe systolic hypertension in the elderly
African-American ethnicity[a]

a Findings are variable.

The characteristic pattern of a high span of BP during the waking period and a low span of BP during the sleep period may be absent or blunted in 10 to 30% of hypertensive patients.[11-13] The term 'dippers' has been used to describe patients whose nocturnal pressure is at least 10% less than their daytime pressure, and 'nondippers' for those for whom the nocturnal decline in BP is blunted or absent.[13] Some of the aetiologies that have been reported for the nondipping BP pattern are shown in table III.

The nondipping pattern of circadian BP variability is clinically important since recent studies suggest that these patients appear to have an increase in cardiovascular morbidity.[12] Conversely, some Japanese studies have suggested that an excessive nocturnal decline of BP, that is more than 20mm Hg lower than daytime pressure, can also be detrimental and related to an increase in cerebrovascular accidents.[14]

While certain secondary causes of hypertension cause blunted or absent nocturnal declines in BP, many patients with the nondipping circadian pattern of BP are primary or essential hypertensives. Little is actually known about the pathophysiology leading to nocturnal hypertension in the essential hypertensive but advanced age and African-American ethnicity may be demographic markers for nondippers.[10,13] In addition, there are data to suggest that hypertensive patients who are salt-sensitive are more likely to be nondippers than patients who are salt-resistant.[13]

3. Circadian Variation of Myocardial Infarction

During the 1980s, epidemiological data demonstrated that acute myocardial infarctions occurred at least 3 times more frequently in the morning than in the late evening (fig. 2).[5,15] In the Thrombolysis in Myocardial Infarction Phase II study (TIMI II),[16] there was a greater frequency of onset of myocardial infarction in the morning, with 34% of episodes occurring between 0600h and noon. It was also noteworthy that some subgroups in this study had even higher rates of morning infarction, including those who had not taken a β-blocking agent within the preceding 24 hours, those who had experienced no chest pain in the past 48 hours, and those who experienced the infarction on a weekday.

In addition to acute myocardial infarction, it has also been reported that sudden death and transient myocardial ischaemia occur with an increased frequency in the morning.[17] As with to the pattern of myocardial infarction onset, Holter ST segment monitoring has shown that transient myocardial ischaemia occurs more often in the first 4 to 6 hours after awakening, a time that typically coincides with initiating activities for the day.[18]

The hypothetical causes of morning increases in the incidence of coronary events are many and include the triggers occurring during the morning awakening period such as increases in physical and mental activity. The well documented increase in early morning BP and HR, as discussed in section 2, increases myocardial oxygen demand. A peaking of catecholamines in the morning hours (see fig. 3) as well as elevation in plasma cortisol levels in combination can increase the sensitivity of the coronary arteries to vasoconstriction.[19]

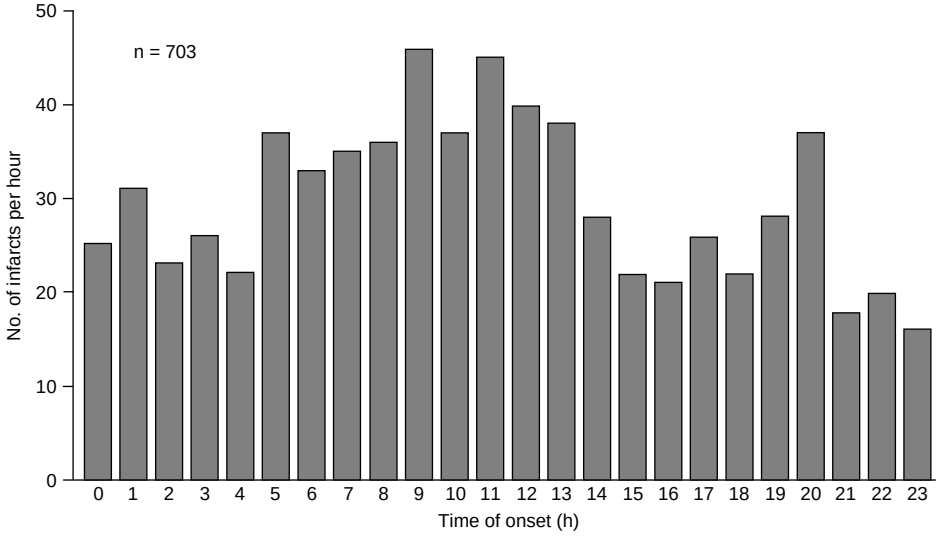

Fig. 2. The circadian pattern of acute myocardial infarction. The data demonstrate an excess incidence of myocardial infarction between 0500h and noon (from Muller et al.,[5] with permission).

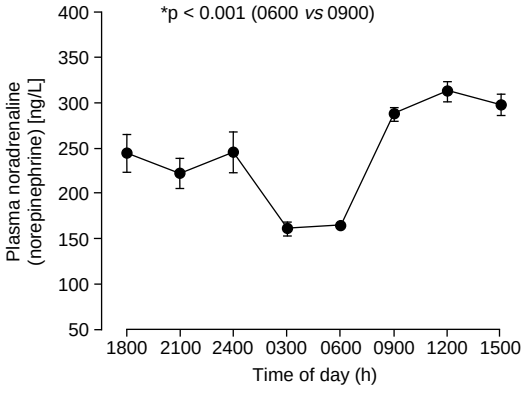

Fig. 3. Morning increases in the catecholamine hormone levels are greatest between 0600h and 0900h and occur simultaneously with increases in platelet aggregability (from Tofler et al.,[19] with permission)

Simultaneously, increases in platelet aggregability, vascular tone and plasma volume occurring in the early morning hours may be involved with reductions in myocardial oxygen supply. A trough of fibrinolytic activity has also been noted to occur in these early morning hours. Together, these various pathophysiological changes can lower the threshold for myocardial ischaemia.[20] Thus, in a susceptible individual with coronary plaque and a high-grade stenosis, early morning plaque rupture followed by thrombosis in the area of the lesion may occlude the vessel, leading to infarction and sudden cardiovascular death.

4. Circadian Variation of Ventricular Arrhythmias

Cardiac arrhythmias have also revealed a circadian rhythm. However, unlike patterns of BP and coronary ischaemia, arrhythmias have not been characterised so thoroughly because of the unpredictability of occurrence and the suboptimal modalities initially used for investigation.

Early studies that utilised 24-hour electrocardiography (Holter) monitoring on a number of occasions to assess the timing of frequent premature ventricular contractions (>30 ectopies/hour) revealed a peak frequency between 0600h and noon.[21,22] For example, in a retrospective study of 68 patients who presented to the hospital with documented ventricular tachycardia,[23] patients were interviewed regarding the onset of cardiac symptoms such as palpitations, presyncope and syncope. The peak occurrence of ventricular tachycardia was demonstrated at 0900h. However, chronobiologists were critical of these early reports as 24 hours was viewed as too short a period to assess a circadian pattern for an arrhythmic event.[24,25]

Recently, precise assessment of the circadian frequency of ventricular arrhythmias was evaluated in a number of studies that used implantable defibrillators which correlated electrical cardioversion, patient diary and RR intervals of the electrocardiogram with the onset of ventricular arrhythmia.[24-28] All of these studies, with the exception of that by Wood and colleagues,[25] demonstrated a peak frequency of ventricular tachycardia or fibrillation at 0600h to noon. The circadian pattern was demonstrated independently of the use of antiarrhythmic therapy. Wood et al.[25] used the same methods of investigation, but noted a peak arrhythmic activity between noon and 1700h.

All of these studies clearly depict a trough of arrhythmogenesis during sleep – a phenomenon known as 'sleep suppression', first described in the early 1970s by Lown et al..[29] Sleep suppression was initially defined as a >50% reduction in nighttime premature ventricular contractions (compared with daytime values). This definition was then carried over to be used in studies of the timing of drug administration and to establish the efficacy of certain antiarrhythmic medications. For example, a study carried out in Italy by Pitzalis and colleagues[30] demonstrated that β-blockers were significantly more efficacious in reducing daytime ventricular ectopy in those patients who had sleep suppression on 24-hour Holters than in those who did not ($p < 0.0001$).

The aetiology that underlies the circadian pattern of ventricular arrhythmias is probably similar to that of other cardiovascular events. The morning surge of circulating catecholamines has been implicated as playing a role in the genesis of cardiac

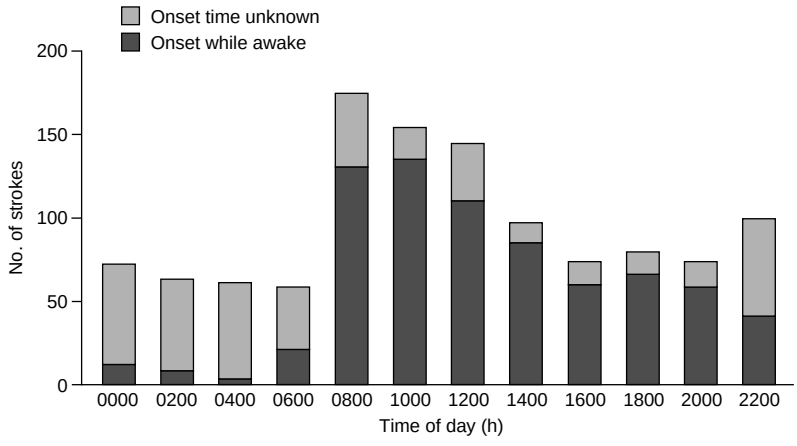

Fig. 4. Onset of ischaemic stroke from 1167 diurnally active patients at 4 medical centres, demonstrating a steep rise in incidence between 0800h and noon. The phenomenon continued to be observed when the frequency was corrected for onset of stroke while awake (from Marler et al.,[6] with permission).

arrhythmias after awakening. Pietrucha et al.[31] demonstrated that a persistent morning peak in cardiac arrhythmias in 42 denervated hearts following heart transplantation could be accounted for by the circulating levels of catecholamine hormones.

Other factors that promote ventricular arrhythmias in patients with coronary disease include an increased HR, a rise in BP and an increase in the incidence of myocardial ischaemia – all well established precursors of ventricular arrhythmias.

In support of the circadian variability of cardiac arrhythmia has been the finding that there is also a circadian variation in defibrillator energy requirements. Venditti and co-workers[28] studied 930 patients with 1238 episodes of ventricular tachycardia, and demonstrated that the frequency of 'first shock failure' was significantly increased during the hours between 0600h and 0900h ($p = 0.0014$). This higher energy requirement was attributed to a number of factors including increases in myocardial ischaemia, a change in posture in the morning resulting in altered electrode orientation and increases in the concentration of plasma adrenaline (epinephrine) [which has been shown to reduce first shock efficacy].[32]

5. Variability of Cerebrovascular Events

As with myocardial infarction and ischaemia, the time of onset of stroke has also been determined to occur considerably more frequently in the first few hours after awakening.[6,20,33,34,35] The main concern regarding the onset of disease was that a number of patients awoke with the neurological deficit, making it difficult to assess the time of onset of disease and therefore a specific circadian pattern.

To overcome this problem, studies quoted in this article evenly distributed those patients who awoke with the symptoms of a stroke over the 8-hour sleep period. Even with this correction, a circadian pattern with an increase in cerebrovascular accidents was noted in the early morning hours. For example, in one large study (n = 1167) conducted in 4 academic medical centre hospitals, Marler and colleagues[6] demonstrated that more ischaemic strokes occurred between 1000h and noon than in any other 2-hour interval (fig. 4). Additionally, the number of patients in whom stroke occurred after awakening (between 0800h and 1000h) significantly exceeded the number expected when controlled for the distribution of the time of onset.

Another large study by Gallerani et al.[34] evaluated the timing of cerebrovascular events in 977

patients and subdivided them into infarctions, haemorrhage and transient ischaemic attacks. All 3 pathological subgroups revealed a peak in event frequency between 0600h and noon.

In a recent case report by Schillaci and colleagues,[36] a patient had the misfortune to experience an ischaemic stroke while wearing a 24-hour ambulatory BP recorder for a hypertension study. In this patient, symptoms of hemiparesis and a visual field deficit occurred approximately 1 hour after the onset of the morning surge in BP and HR.

Not surprisingly, studies of haemorrhagic stroke[37-40] have also shown a propensity for a higher proportion of events in the late morning hours. In a study by Sloan and co-workers,[39] patients with cerebrovascular haemorrhage were subdivided into those with intracerebral haemorrhage versus those with subarachnoid haemorrhage. In the 237 patients with intracerebral haemorrhage, there was a significant peak in onset between 1000h and noon even after randomly distributing patients who awoke with the symptoms between midnight and 0800h. However, those with subarachnoid haemorrhage had onset of symptoms more evenly distributed throughout the day. The difference between the groups was attributed to the fact that patients with intracerebral haemorrhage were more likely to be hypertensive ($p < 0.001$) than the subarachnoid haemorrhage patients.

In addition, Kleinpeter et al.[40] recently studied 273 patients with subarachnoid haemorrhage and subdivided them into hypertensive and normotensive populations. A definite circadian rhythm with a peak event rate between 0800h and 1000h was observed in the hypertensive group, while there was no distinct circadian rhythm noted in the normotensive group. No relationship has been demonstrated between the site or size of intracerebral haemorrhage and the time of onset of symptoms.[39]

In some hypertensive populations, the extent of nocturnal decline in BP has been shown to be related to ischaemic cerebrovascular disease.[38] Using specialised T-1 and T-2 weighted magnetic resonance imaging of the brain, Kario and coworkers[14] in Japan have demonstrated that older (average age 70 years) hypertensive patients who are nondippers or whose nocturnal BP declines more than 20% compared with average waking levels have a greater prevalence of silent cerebrovascular lesions (lacunar infarctions and periventricular ischaemic lesions) than those whose nocturnal decline is within 10 to 20% of waking levels (table IV).

In addition, Nakamura et al.[41] have analysed the circadian BP in 76 patients who had experienced a prior cerebrovascular accident. They observed that dippers (defined as those with a >10mm Hg drop in mean arterial BP during sleep on ambulatory BP monitoring) who were on antihypertensive medication (n = 18) had a significantly higher incidence of recurrence of symptomatic and silent cerebrovascular accidents than untreated dippers (n = 10) or all nondippers (n = 48). Silent events were monitored by performing a second magnetic resonance image of the brain and com-

Table IV. Silent target-organ damage and metabolic characteristics of elderly patients according to extent of nocturnal blood pressure fall (from Kario et al.,[14] with permission)

	Extreme dippers[a] (>20%)	Dippers (>10-<20%)	Nondippers (<10%)
Lacunae (n)	2.9 (1.1-4.7)*	1.2 (0.4-1.9)	2.3 (1.6-3.1)*
(%)	69†	32	63**
Advanced cerebral ischaemia (%)	50†	18	41*
ECG-LVH (%)	25	21	44*
Urinary albumin (μg/min)	21 (15-32)	20 (14-27)	30 (22-41)*
Microalbuminuria (%)	69	50	78†

a See section 2 for definition.

Abbreviation and symbols: ECG-LVH = left ventricular hypertrophy on electrocardiogram; *$p < 0.05$, †$p < 0.02$, **$p < 0.02$ *vs* dippers.

Table V. Methods for the analysis of ambulatory blood pressure (BP) data (from White,[42] with permission)

24h means (and standard deviation as measure of variability)
Waking and sleeping means (derived from patient activity journals)
Hourly or block-time means
BP load (proportion of BPs >140/90mm Hg while awake and >120/80mm Hg during sleep)
Area under the BP curve
Placebo-subtracted BP curves showing hourly means
Data smoothing (e.g. Fourier transformations, spline curves)
Cusums analyses

paring it with the baseline study done at the start of the trial.

These data raise the concern that excessive BP reduction during sleep may predispose hypertensive patients with underlying atherosclerotic vascular disease to ischaemic events in the brain. However, the findings noted by Japanese investigators may not necessarily be representative of a general population in another country.

6. Evaluation of Antihypertensive Therapy by Ambulatory Monitoring of Blood Pressure

There are a number of advantages to using ambulatory monitoring of BP for assessing antihypertensive therapy. Ambulatory BP recording allows us to assess the effect of a drug in the patient's own environment over a 24-hour period by obtaining 75 to 100 BP and HR measurements, and also to eliminate bias from the 'white coat effect'. From a clinical trialist's perspective, it also helpful that ambulatory BP is much less susceptible to the effects of placebo and observer bias than the clinic or office BP.[42,43]

Data from the ambulatory BP study may be analysed in a variety of ways (table V). The use of measures of centrality, such as the 24-hour means, daytime and nocturnal means (preferably waking or sleeping values), BP loads, area under the 24-hour BP curve and correlating BP with activity levels, are the most widely used methods of analysis.

The reproducibility of 24-hour ambulatory BP is superior to clinic or casual BP measurements,[9,11] but the reproducibility of a single hour of the ambulatory BP is not.[25] Thus, when examining a portion of the BP curve, such as a 4-hour period after awakening, a large sample size is typically required to study the effect of a drug on the morning surge of BP.

7. Chronotherapeutics for Cardiovascular Disease

A major objective of chronotherapy for cardiovascular diseases would be to deliver the drug in higher concentrations during the time of greatest need, e.g. the early morning postawakening period, and in lesser concentrations when the need is less, e.g. during the middle of the sleep cycle. At present, there are not enough data to know whether altering the administration time of an antihypertensive or antianginal therapy, which is conventionally administered once daily in the morning, would achieve these objectives.

Recently, a few studies have evaluated the effects of the timing of the dose of a conventional antihypertensive agent on circadian BP – for example, morning versus evening administration of a once-daily agent.[44-49] However, the results of these relatively small studies have been inconsistent.

In a seminal study[44] in which the ACE inhibitor quinapril was administered in the early morning versus at bedtime in 18 moderately hypertensive

Table VI. Effects of morning versus evening administration of quinapril in patients with hypertension (from Palatini et al.,[44] with permission)

Time of measurement	Blood pressure (mm Hg)		
	placebo	morning quinapril	evening quinapril
Daytime			
SBP	154 ± 16	138 ± 16	137 ± 14
DBP	101 ± 7	89 ± 9	90 ± 9
Night-time			
SBP	140 ± 15	132 ± 20	127 ± 18**
DBP	90 ± 7	83 ± 10	81 ± 9*

Abbreviations and symbols: DBP = diastolic blood pressure; SBP = systolic blood pressure; *p < 0.05, **p < 0.01 *vs* morning administration.

Table VII. Crossover studies comparing morning and evening administration of a variety of conventional antihypertensive medication (from Lemmer,[48] with permission)

Drug	Dosage (mg/day)	Duration (wk)	Time of administration (h)	No. of patients	Diagnosis	Effect on baseline BP			Reference
						day	night	24h pattern	
Calcium antagonists									
Amlodipine	5	4	Morning	20	EH	↓↓	↓↓	Unchanged	48
			Evening			↓↓	↓↓	Unchanged	
Isradipine	5	4	0700	18	EH	↓↓	↓↓	Unchanged	50
			1900			↓↓	↓↓	Unchanged	
	5	4	0800	16[a]	RH	↓↓	↓	Not normalised (still dippers)	51
			2000			↓(↓)	↓↓(↓)	Normalised (dippers)	
Nifedipine GITS	30	1 *or* 2	1000	10	EH	↓↓	↓↓	Unchanged	46
			2200			↓↓	↓↓	Unchanged	
Nitrendipine	20	4	0700	41	EH	↓	↓	Unchanged	52
			1900			↓	↓	Unchanged	
	10	3 days	0600	6	EH	↓↓	↓↓	Unchanged	53
			1800			↓	↓↓	Changed	
ACE inhibitors									
Benazepril	10	SD	0900	10	EH	↓↓↓	↓↓	Nearly unchanged	54
			2100			↓	↓↓	Changed	
Enalapril	10	SD	0700	10	EH	↓↓	↓	Nearly unchanged	55
			1900			↓↓	↓↓↓	Changed	
		3	0700			↓↓	(↓)	Nearly unchanged	
			1900			↓	↓↓	Changed	
Quinapril	20	4	0800	18	EH	↓↓	↓	Nearly unchanged	44
			2000			↓↓	↓↓	Changed	

a Nondippers (see section 2 for definition) at baseline.

Abbreviations and symbols: ACE = angiotensin converting enzyme; BP = blood pressure; EH = essential hypertension; GITS = gastrointestinal therapeutic system; RH = renal hypertension; SD = single dose; ↓ = decrease in blood pressure relative to baseline (number of symbols proportional to size of decrease).

patients, it was demonstrated that nocturnal administration of the drug yielded substantially greater effects on nocturnal pressure than morning administration (table VI). There was no significant difference in daytime BPs. Measurement of ACE activity showed that nocturnal administration of quinapril induced a more sustained decline in plasma ACE. The greater decline in nocturnal pressures (i.e. an increase in 'dipping') may be detrimental in the elderly or in subjects who have already had a cerebrovascular event.[14,41]

In contrast to the study of quinapril, a study of the β-blocker atenolol[45] and the dihydropyridine calcium antagonists nifedipine GITS[46]and amlodipine[47] showed no differential effects on BP whether these drugs were given in the morning or the evening. However, these studies had relatively small sample sizes and may have been underpowered to demonstrate equivalence of the effect of administration times on 24-hour, waking or sleeping BP.

Lemmer[48] recently provided a review on the impact of administration time of antihypertensive therapy. Several crossover studies were reviewed that generally depicted unchanged circadian patterns when comparing morning and evening administration of a variety of the conventional antihypertensive agents (table VII).

The first chronotherapeutic agent for hypertension[56,57] and angina pectoris[58] was recently de-

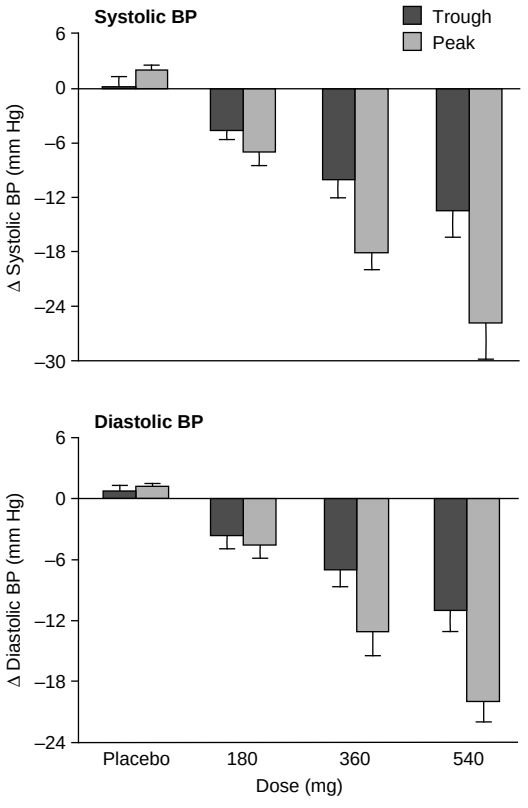

Fig. 5. Effects of 3 doses of the chronotherapy, controlled onset extended release verapamil (COER-24), versus placebo on trough (evening) and peak (early morning) systolic and diastolic BP after 8 weeks of therapy in 287 hypertensive patients (from White et al.,[56] with permission).

veloped and marketed to match drug delivery to the circadian BP and myocardial ischaemia rhythms. The cardiovascular drug verapamil has been placed in this novel delivery system [controlled onset, extended release (COER-24)] that has a delay in release of approximately 4 to 5 hours after administration and then has an extended release for approximately 18 hours. When taken at bedtime, the delivery system provides optimal drug concentrations between 0400h to 0500h and noon, a period of time when both BP and HR rise in association with awakening and increased physical activity. Thus, haemodynamic effects (both BP and HR) are substantial during the early morning (the peak period), remain clinically effective during the daytime, and are smaller during sleep (the trough period) when cardiovascular demands are less (fig. 5).

A *post hoc* analysis of the effects of COER-24 verapamil on the rate of rise of BP and HR in the early morning hours (0400h to 1000h) was compared with placebo therapy.[8] The haemodynamic data were derived from the 24-hour BP recordings at baseline and following 8 weeks of treatment. The mean slope (rate of rise) was calculated for the various dosage groups and compared by analysis of covariance. The rate of rise of systolic and diastolic BP was reduced at doses of verapamil 180 and 540mg compared with placebo. Furthermore, there was a significant reduction in the slope of the HR rise at all doses of COER-24 verapamil compared with placebo (fig. 6).

The effects of COER-24 verapamil have also been studied in patients with angina pectoris using time on the treadmill to achieve moderate levels of angina pectoris or the time to achieve >1mm ST-segment depression on the electrocardiogram[58] as the primary efficacy end-point. Exercise treadmill tests were scheduled both at peak effect times (between 0700h and 1000h) and trough effect times (1800h and 2200h). While in both cases the drug was statistically more effective than placebo, there were enhanced benefits in the early morning hours (fig. 7).

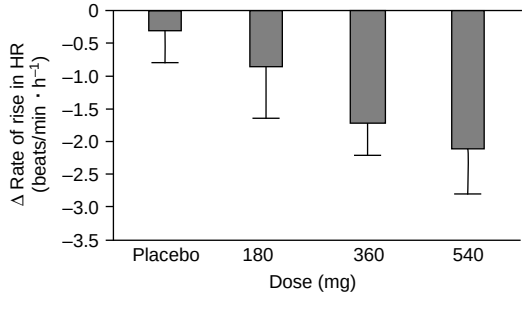

Fig. 6. The effects of different doses of controlled onset extended release verapamil (COER-24) on the rate of rise of heart rate (HR) in the early morning hours (between 0400h and 1000h). The slope of the rise was significantly lowered with the intermediate and higher doses of the drug; *$p < 0.005$; **$p < 0.001$ (from White,[8] with permission).

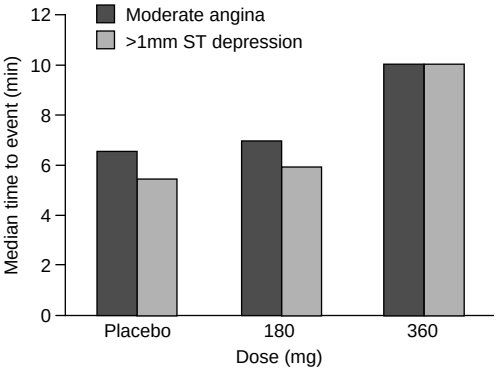

Fig. 7. Effects of controlled onset extended release verapamil (COER-24) in patients with angina pectoris. The drug significantly improved exercise time to the development of angina and ST segment depression during stress tests performed in the early morning hours (0700h to 1000h); *p < 0.05; **p < 0.01 (from Cutler et al.,[57] with permission).

8. Other Potential Chronotherapies in Cardiovascular Disorders

Small-scale studies regarding the anticoagulant effect of heparin have also been carried out. In 1985, Decousus et al.[59] demonstrated that there was a 50% reduction in mean activated partial thromboplastin time (APTT) at 0800h versus 2000h in patients receiving constant infusions of intravenous heparin. These data suggested that an independent circadian variation in coagulation is operative. The clinical implications of this, if accurate, are important, as patients could be subtherapeutic on constant heparin infusion at times when they are at highest risk of experiencing thromboembolic events, or it could be overeffective at other times of the day with the risk of haemorrhage. However, this finding has not been universally observed.[60] Thus, further research in the area of chronotherapeutics of anticoagulation is certainly needed.

9. Implications for Chronotherapy of Cardiovascular Diseases

The data from the Controlled ONset Verapamil INvestigation of Cardiovascular End-points (CONVINCE) trial, an international study dealing with COER-24 verapamil, will demonstrate whether antihypertensive, antianginal therapy can be designed to provide reductions in myocardial infarction and stroke that closely follow the circadian rhythms. The verapamil formulation was developed for bedtime administration because it has a delay in drug release so that appearance of the drug occurs before early morning awakening. The implications of this type of guided therapy may be substantial since a number of studies have shown that cardiovascular events occur frequently in the early morning hours, in association with increases in BP, HR, cardiac ischaemia, enhanced platelet aggregability and increases in plasma catecholamines.[1,17,37]

Chronotherapy links the biological effects of a disease associated with time and the timing of drug delivery. However, it has not yet been recommended as a therapy of choice by various health organisations such as the WHO or the US Joint National Committee V or VI. Future research in the area of the chronotherapeutics of cardiovascular diseases will evaluate whether timing of drug delivery has an effect on outcomes, including heart attack and stroke.[61] In the meantime, comparative clinical trials are needed that evaluate the effects of chronotherapeutic versus homeostatic antihypertensive or anti-ischaemic therapies on clinical endpoints, including improvement in BP values, quality of life, silent ischaemia and cardiac function.

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Correspondence and reprints: Professor *William B. White,* School of Medicine, University of Connecticut Health Center, Section of Hypertension and Clinical Pharmacology MC-3940, 263 Farmington Avenue, Farmington, CT 06032-3940, USA.