Circadian variations in cardiovascular disease

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■ Circadian variations have been observed for a number of hemodynamic and cardiovascular events including heart rate, systemic blood pressure, coronary artery blood flow, ischemic cerebrovascular accidents, myocardial ischemia, myocardial infarction, and sudden cardiac death. In addition, circadian variations in platelet response to aggregating stimuli, plasma fibrinogen, coagulation factor concentration, and intrinsic fibrinolytic activity (as determined primarily by inhibitors of plasminogen activation) have been documented. Observed periodicities in thrombogenic capacity and cardiovascular events seem to correlate directly, suggesting a cause-effect relationship. Circadian variations in thrombotic tendency may influence the therapeutic response to anticoagulants and thrombolytic agents, particularly rt-PA. This area of cardiovascular disease is of profound clinical importance and warrants further investigation.

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THAT period of 24 hours, formed by the regular revolution of the earth, in which all its inhabitants partake, is particularly distinguished in the physical economy of man.... It is the unity of our natural economy.—C.W. Hufeland, *The art of prolonging life* [1797][1]

Circadian variation (rhythm, periodicity) refers to a dynamic state in which biological systems change predictably and consistently over a 24-hour period, unique from fluctuations expected on the basis of temperature change and light-dark cycles. In humans, circadian variations have been identified for more than 100 psychologic and physiologic variables including adrenal, sympathetic/parasympathetic, hypothalamic, and pituitary activity. Therefore, all levels of metabolic function may be influenced.[2]

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This review discusses circadian variations of cardiovascular disease, with particular emphasis on thrombus formation in the pathogenesis of myocardial infarction, daily fluctuations in thrombotic tendency, and its potential influence on treatment response.

CIRCADIAN VARIATION IN HEMODYNAMIC AND CARDIOVASCULAR EVENTS

Circadian variations in hemodynamic parameters and cardiovascular events have been identified (*Table 1*). Daily fluctuations in heart rate, independent of physical activity, reflect similar variations in adrenal and sympathetic nervous system activity.[3] Neurohumoral activation is also the mechanism underlying changes in systemic blood pressure.[4] Continuous intraarterial monitoring has shown that systolic and diastolic blood pressures are lowest at 3 AM and highest at 10 AM.[4]

Thrombotic stroke is most frequently diagnosed in the late morning hours. Robertson et al[5] used the Stroke Data Bank, a multicenter trial initiated by the National Institute of Neurologic and Communicative Disorders and Stroke, to analyze the time of symptom onset for

TABLE 1
CIRCADIAN VARIATIONS IN CARDIOVASCULAR DISEASE

Cardiac Event	Time of peak level
Heart rate	0900–1200
Blood pressure	1000
Stroke	0900–1200
Arterial embolization	0800–1600
Myocardial blood flow	1600
Myocardial ischemia	0600–1200
Myocardial infarction	0600–1200
Sudden cardiac death	0600–1200

1700 cases of confirmed stroke. The frequency was lowest in the early morning hours and highest between 9 AM and noon.[5] In-hospital progression of defined neurologic deficits also followed this pattern. Patients with mitral valve disease, particularly those with atrial fibrillation, are more likely to experience symptomatic arterial embolization between 8 AM and 4 PM than during other time intervals.[6]

The dynamic nature of intravascular blood flow has prompted investigators to search for a circadian variation in coronary blood flow. Indeed, coronary blood flow velocity, as determined with Doppler flow probes in dogs, is significantly lower between 8 and 9 AM than at other times of the day or night.[7] Such changes are independent of heart rate, blood pressure, left-ventricular end-diastolic pressure, peak dP/dt, end-diastolic regional myocardial dimension, and regional myocardial stroke work.[7] A circadian variation in vasomotor tone has also been identified in patients with coronary arterial spasm (Prinzmetal's angina),[8] which may involve periodicities in parasympathetic nervous system outflow.[9–11]

Patients with ischemic coronary heart disease frequently experience angina pectoris in the morning hours after awakening from sleep. Exercise-related ST segment depression, as observed during diagnostic exercise tolerance testing, occurs at lower heart rates in the morning compared with the afternoon.[12] Continuous ambulatory monitoring in patients with known coronary artery disease has allowed identification of a circadian variation in ischemic ST-segment events occurring between 6 AM and noon.[13] As with changes in myocardial blood flow, these events are independent of determinants of myocardial oxygen demand such as heart rate, blood pressure, and physical activity.

The observed circadian variations in myocardial blood flow, intravascular thrombotic events, and myocardial ischemia has prompted investigations of similar periodicities in myocardial infarction and sudden cardiac death. Numerous epidemiologic studies performed in Europe,[14,15] Hungary,[16] Sweden,[17] Great Britain,[18,19] the Soviet Union,[20] and the United States[21,22] have documented a peak symptom onset for myocardial infarction between 6 AM and noon. An identical circadian variation has been identified in the frequency of sudden cardiac death, defined as death from cardiac disease occurring less than or equal to 1 hour after the onset of symptoms.[23–26]

THROMBOGENESIS AND CORONARY HEART DISEASE

The major pathophysiologic event underlying acute coronary syndromes, including myocardial infarction, is intracoronary thrombosis. Coronary angiography performed during the early stages of an evolving transmural infarction (less than 4 hours from symptom onset) reveals complete vessel occlusion in an overwhelming majority of cases.[27] Given this important fact, two questions must be addressed: "Are individuals with coronary heart disease predisposed to intracoronary thrombosis?" and if so, "Are there circadian variations in thrombotic tendency?"

Coronary atherosclerosis with resulting endothelial disruption, cross-sectional luminal narrowing, and alterations in laminar blood flow increases the likelihood of thrombus formation through a number of local mechanisms including enhanced platelet activation, decreased vascular PGI_2 synthesis/release, decreased endothelial-derived relaxing factor (EDRF) synthesis/release, and decreased plasminogen activator synthesis/release. In addition, patients with coronary heart disease, including those with chronic stable angina, accelerated angina, and/or nonfatal myocardial infarction, frequently exhibit systemic abnormalities in the hemostatic mechanism that predispose them to intracoronary thrombosis. A significant increase in serum fibrinogen and plasminogen activator inhibitor (PAI), coupled with a decrease in t-PA antigen and activity, may explain the enhanced capacity to form, and decreased capacity to lyse, blood clots in these patients.[28–34]

Daily variations in plasma fibrinogen, platelet aggregation, partial thromboplastin time (PTT), thrombin time (TT), and serum antithrombin III concentration have been observed in both patients with vascular disease and healthy controls. The tendency toward thrombus formation, as reflected by these parameters, is more pronounced in patients with vascular disease and, in fact, normal circadian variations may be attenuated.[35] In vitro platelet response to aggregating stimuli, such as adenosine diphosphate (ADP) and epinephrine, is ac-

TABLE 2
TIME OF THROMBOLYTIC THERAPY AND RESPONSE RATES

	Patients		Lysis (+)		Lysis (–)		% Success		
Time of Treatment	SK	rt-PA	SK	rt-PA	SK	rt-PA	SK	rt-PA	*P* Value*
0000–0600	1	2	1	0	0	2	100	0	ns
0600–1200	6	9	4	3	2	6	67	33	ns
1200–1800	11	12	7	9	4	3	64	75	ns
1800–2400	2	5	1	5	1	0	50	100	ns
Total	20	28	13	17	7	11	65	61	ns
0000–1200	6	11	5	3	1	8	83	27	ns
1200–2400	14	17	8	14	6	3	57	82	ns

SK = streptokinase; *rt-PA* = recombinant tissue-type plasminogen activator; *ns* = not statistically significant.
* = 2-sided (differences in lysis between SK and rt-PA for each time interval).
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TABLE 3
COMPARISON OF RATES OF THROMBOLYSIS FOR rt-PA BETWEEN TREATMENT TIME INTERVALS

Time	% Lysis		Time	% Lysis	*P* Value*
0000–0600	0	vs	0600–1200	33	ns
0000–0600	0	vs	1200–1800	75	ns
0000–0600	0	vs	1800–2400	100	.0477†
0600–1200	33	vs	1200–1800	75	ns
0600–1200	33	vs	1800–2400	100	.0310†
1200–1800	75	vs	1800–2400	100	ns
0000–1200	27	vs	1200–2400	82	.0062†
0600–1800	57	vs	1800–0600	71	ns

ns = not statistically significant.
* = 2-sided.
† = statistically significant.
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centuated during the morning hours, particularly after arising from sleep.[36,37] Similar variations in platelet receptor binding affinity (alpha$_2$-adrenoreceptor) may explain this finding.[38]

Systemic fibrinolytic activity, as measured by fibrin plate analysis, undergoes daily fluctuations with lowest activity at 8 AM and highest between 5 and 8 PM.[39,40] Increased fibrinolytic activity following physical exercise is attenuated during the morning hours, most likely due to an increased serum PAI concentration during this period.[40–43]

Circadian variations in serum PAI concentration have been observed in patients with angiographically documented coronary heart disease, with peak levels occurring between 6 and 8 AM.[44,45] Patients with unstable angina pectoris have similar variations and, moreover, have been shown to have an elevated serum PAI concentration in samples taken immediately preceding evolution to acute myocardial infarction.[45] Fibrinolytic activity commonly shows an inverse correlation with serum PAI concentration, reflecting its potentially critical role in overall hemostatic balance.[46]

TREATMENT: CIRCADIAN VARIATIONS AND RESPONSE TO THROMBOLYTIC AGENTS

As discussed, patients with coronary heart disease have a marked predisposition to intracoronary thrombosis. The daily fluctuation in serum coagulation factors, platelet aggregability, and fibrinolytic capacity may be the pathophysiologic substrate of observed thrombotic events. As therapeutic options for myocardial infarction evolve, circadian variations in thrombotic tendency and response to thrombolytic therapy must be explored.

In patients with venographically documented venous thrombosis, systemic anticoagulation with continuous intravenous heparin, as assessed by the PTT, TT, and factor Xa inhibition assay, follows a circadian variation

with maximum values at night and minimum values in the morning.[47] Since night and morning values may vary by as much as 50%, daily dose adjustments may prove to be warranted to avoid periods of excessive or inadequate systemic anticoagulation.[47]

The potential influence of serum PAI concentration on treatment response to thrombolytic agents, particularly recombinant tissue plasminogen activator (rt-PA), is receiving increased attention. Fibrin clots prepared from endogenous t-PA-rich plasma lyse spontaneously within a few hours, whereas clots prepared from t-PA-poor plasma do not undergo spontaneous lysis, nor do they lyse with the addition of exogenous t-PA.[48,49] This finding suggests that incorporation of endogenous t-PA into a clot as it forms is a prerequisite for subsequent lysis and that a reduced concentration of endogenous t-PA (or an elevated concentration of PAI) could impair the lytic response to exogenous rt-PA.

THROMBOLYTIC RESPONSE TO rt-PA IN ACUTE MYOCARDIAL INFARCTION

Under normal conditions, the overall effect of serum PAI concentration on thrombolytic response to rt-PA in acute myocardial infarction appears to be minimal, given the doses currently used in clinical practice and the serum t-PA antigen concentrations achieved.[50] However, a number of critical points must be considered: patients with coronary heart disease frequently have significantly elevated PAI activity[30,32–34]; latent PAI exists in plasma and may become activated following cell-surface binding[51]; the local concentration of PAI in the area of thrombotic occlusion may be markedly elevated as a result of endothelial, subendothelial, and platelet release.[52–55] Furthermore, patients receiving intravenous rt-PA as therapy for acute myocardial infarction have been shown to exhibit a marked decrease in serum t-PA activity, coupled with an increase in serum PAI activity, following completion of the rt-PA infusion.[56,57] Inefficient plasminogen activation, possibly the result of an elevated serum PAI concentration, may also explain the variability in fibrinolytic activity and clinical response in patients receiving intravenous rt-PA.[58] Furthermore, the ability to decrease serum PAI concentration pharmacologically and subsequently increase t-PA activity supports the potential modifying role of PAI in thrombolytic treatment response.[59]

Our interest in circadian variations in cardiovascular disease prompted an investigation to identify periodicities in thrombolytic response to either intravenous streptokinase or rt-PA. Forty-eight patients with angiographically documented subtotal or total coronary occlusion were randomly assigned to thrombolytic treatment during the early stages of acute myocardial infarction. Coronary artery reperfusion was assessed with serial coronary injections over a 90-minute period. In patients receiving streptokinase, coronary reperfusion was equally likely, regardless of the time of day when treatment was begun (*Table 2*). However, in patients treated with rt-PA between midnight and noon, reperfusion was four times less likely than in patients treated at other times of day (*Table 3*).[60]

While t-PA antigen, t-PA activity, and PAI concentration were not measured in this study, the recognized variations in fibrinolytic activity in patients with coronary heart disease during the morning hours suggests that our observation, at the very least, requires further investigation. If verified, its clinical implications would be significant.

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