Circadian Variation in Ischemic Threshold
A Mechanism Underlying the Circadian Variation in Ischemic Events

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Evidence has accumulated recently indicating that there is a circadian pattern in the occurrence of many cardiovascular events. Transient myocardial ischemia, detected by ambulatory ST segment monitoring, is unevenly distributed during the day.1-4 There is a rise in the frequency of episodes in the morning after awakening that reaches a peak within 1–2 hours, plateaus until noon, and gradually decreases thereafter. There is a possible secondary evening peak around 6–8 PM, and the least number of episodes occur at night. A similar circadian pattern of distribution of events has also been described for myocardial infarction,5 sudden cardiac death,6 and ischemic stroke.7

The mechanisms underlying this uneven distribution of transient myocardial ischemia are unknown, but changes in two determinants of myocardial oxygen demand8 (i.e., heart rate and blood pressure), which also follow a similar circadian distribution, may be at least partly responsible. Neural and humoral vasoactive factors also exhibit a circadian pattern of distribution; for example, plasma norepinephrine level9 and plasma renin activity,10 both important mediators of vasoconstriction, are higher in the morning hours and may cause coronary vasoconstriction. It is thus possible that a circadian variation in coronary vascular tone contributes to the observed variation in ischemic episodes. The present study was undertaken to determine whether there is a circadian variation in ischemic threshold in patients with coronary artery disease and, if so, whether it relates to a circadian variation in vascular tone.

Methods

Patients
We studied 31 patients (28 men and three women) between 49 and 72 years of age (mean, 62±1.1 years) with stable coronary artery disease. All had angiographically proven significant coronary stenosis (≥70%) involving
one or more major coronary arteries and developed ≥1-mm ST segment depression during treadmill exercise testing. Seven patients had New York Heart Association class II symptoms, and the remaining were asymptomatic; none had suffered a recent myocardial infarction or acute exacerbation of symptoms in the preceding 6 months. Forearm blood flow studies, treadmill exercise, and ambulatory monitoring were performed after withdrawal of all antianginal medications for at least 48 hours.

Protocol
The first group of 15 patients (group A) underwent treadmill exercise testing at 8 AM, noon, 5 PM, and 9 PM. Before each exercise, patients had forearm blood flow measured in the supine position at rest and after 5 minutes of forearm ischemia. Arterial blood pressure was measured with a sphygmomanometer in this study. Also, to minimize the effects of training during repeated exercise, the study was begun in the morning in four patients, at noon in four patients, at 5 PM in four patients, and at night in three patients.

The reduced heart rate–ischemic threshold in the mornings could be the result of a true reduction in the maximal capacity of the coronary vasculature to vasodilate at this time of the day. However, it has been shown that the rate–pressure product more closely approximates myocardial oxygen consumption than does heart rate alone, and changes in rate–pressure product at the onset of ischemia would therefore more closely reflect ischemic threshold. Furthermore, if the blood pressure is higher in the morning, then the true ischemic threshold may not actually be lower in the morning even though the heart rate is lowest at this time. The reason for this is that the higher blood pressure would offset the lower heart rate, and thus, the rate–pressure product at ischemia, a reflection of the lowest coronary vascular resistance, would be the same at all times of the day.

To investigate this issue, in another group of 16 patients (group B), we performed treadmill exercise testing twice in one day, one at 8 AM and the second at 1 PM. During this study, blood pressure was monitored continuously using an intra-arterial line. To overcome the effects of any psychological stress related to the first exposure to an unfamiliar study, all patients underwent at least two treadmill exercise tests before the day of the study and had forearm blood flow measured once beforehand.

Treadmill Exercise Testing
Symptom-limited graded treadmill exercise testing was performed using the combined National Institutes of Health (NIH) protocol11 in all group A patients undergoing four exercise tests. A 12-lead ECG was recorded at rest and at 30-second intervals until the onset of limiting chest pain, fatigue, or ≥3-mm ST segment depression. Blood pressure was measured with a sphygmomanometer at the end of each stage. A positive exercise test was defined when ≥1-mm ST segment depression occurred 0.08 seconds after the J point, lasting for ≥1 minute. Ischemic threshold in this study was defined as the heart rate at the onset of 1-mm ST segment depression (heart rate–ischemic threshold).

In group B patients who underwent two exercise tests, blood pressure was monitored continuously using an intra-arterial line; nine patients were exercised using the Bruce protocol, and the remaining were exercised using the combined NIH protocol. Both the 12-lead ECG and blood pressure were recorded at 30-second intervals. It was thus possible in group B patients to measure the ischemic threshold as the heart rate–blood pressure product at the appearance of 1-mm ST segment depression (rate–pressure product–ischemic threshold). Analysis of all tests was performed by two independent observers who were not aware of the times of the exercise tests.

Forearm Plethysmography
Subjects were studied in the supine position in a quiet room at a temperature of approximately 22°C (72°F). The dominant arm was slightly elevated above the level of the right atrium, and a mercury-filled Silastic strain gauge was placed about 7 cm below the antecubital fossa on the widest part of the forearm. This was connected to a plethysmograph (DE Hokanson, model EC-4, Issaquah, Wash.) calibrated to measure the percentage change in volume, which was connected to a Gould chart recorder for forearm flow measurements12. With a blood pressure cuff on the upper arm inflated to 40 mm Hg, using the rapid cuff inflator (DE Hokanson, model E-10) to occlude venous outflow from the extremity, forearm blood flow was recorded. To exclude hand circulation, a wrist blood pressure cuff was inflated to suprasystolic pressures 1 minute before the new recordings were made. All blood pressures were recorded in the contralateral arm by sphygmomanometry 1 minute before release of the occluding cuff.

To evaluate the hyperemic response to forearm ischemia, the blood pressure cuff on the upper arm was inflated to 190 mm Hg, thereby occluding the circulation to the forearm. After a 5-minute period of ischemia, the occluding cuff was rapidly deflated to 0 mm Hg and reinflated to 40 mm Hg, with flow measurements taken 5 seconds after the rapid deflation. Postischemic measurements were obtained in duplicate with at least a 15-minute period between the two measurements. Postischemic vascular resistance was calculated as the mean arterial pressure (mm Hg) divided by forearm blood flow (in ml/min/100 ml tissue). Mean pressure was estimated as ½(systolic blood pressure minus diastolic blood pressure) plus diastolic blood pressure.

Ambulatory ST Segment Monitoring
All patients underwent outpatient ambulatory ST segment monitoring and kept detailed diaries of their activities and symptoms. A total of 3,220 hours of monitoring were performed in 31 patients (mean, 104±16 hours per patient). Eight patients had monitoring for 24 hours, nine for 48 hours, three for 96 hours, and the other nine for 5 days or more. After careful skin preparation, bipolar lead CM5 and modified lead II were monitored. Recordings were made initially in the erect, supine, prone, left and right lateral positions, and during hyperventilation, and patients who developed significant ST segment change with these maneuvers were excluded. The tapes were analyzed visually and automatically at ×60 and ×120 normal speed using the
Delmar Avionics 750-A system. Real-time printouts at a paper speed of 25 mm/sec were obtained before, at the onset, and during maximum ST segment depression. An ischemic episode was defined as ≥1-mm ST segment depression at 0.06 seconds after the J point and lasting ≥1 minute. Return of the ST segment to baseline for at least 3 minutes was required between two episodes. Changes in T wave morphology alone were not considered to be indicative of ischemia.

Statistical Analysis

Results are expressed as mean±SEM. To investigate differences in the forearm vascular tone or the ischemic threshold according to the time of day in group A patients, a two-way ANOVA was used to compare the effect of the four specific times of day (this can also be considered as a randomized block design with the individual as the block and time as the treatment). To control the significance level at 0.05 while allowing for all pairwise comparisons of the times of day, the Bonferroni method of adjustment for multiple comparisons was used.

To determine whether a relation exists between the ischemic threshold and either the postischemic forearm blood flow or resistance irrespective of time of day, a linear regression model was used, with ischemic threshold as the dependent variable and forearm blood flow or resistance and the individual as independent variables (individual was included as a classification variable). Finally, to compare ischemic threshold in group B patients undergoing two exercise tests, and to compare the number of ischemic episodes in the day versus the night, the Student's t test was used, and a value of p<0.05 was considered statistically significant.

Results

Variation in Ischemic Threshold

In group A patients, who underwent four exercise tests per day, the heart rate at the onset of 1-mm ST segment depression (ischemic threshold) in individual patients varied by 10±1% (range, 2–16%) at different times of the day. A circadian pattern was noted whereby the ischemic threshold was lower in the morning (8 AM) and at night (9 PM) compared with noon and 5 PM (p=0.03) (Figure 1). When individual patient responses were examined, ischemic threshold was lowest in the morning (8 AM) in nine patients, at night (9 PM) in four patients, and at noon in two patients.

To demonstrate that the lower heart rate threshold in the mornings was also reflected as a reduced heart rate–blood pressure threshold, we studied 16 additional patients (group B) who underwent two exercise treadmill tests, one at 8 AM and the second at 1 PM. Blood pressure was measured continuously using an intraarterial line, so that ischemic threshold in this group could be measured as the heart rate–blood pressure product at the development of 1-mm ST segment depression. There was a mean 8±2% (range, 0–31%) variation in the ischemic threshold between the two studies in group B (Figure 2), with the ischemic threshold being significantly lower in the morning compared with 1 PM (p<0.003). Fourteen of the 16 patients (group B) had a lower ischemic threshold at 8 AM compared with 1 PM. This study thus confirmed findings in group A patients who demonstrated a reduced heart rate–ischemic threshold in the morning and indicates that there is a true reduction in the ischemic threshold in the morning.

Variation in Postischemic Forearm Blood Flow and Resistance

In group A, postischemic forearm vascular resistance varied by a mean of 40±10% (range, 13–110%) at different times of the day. There was a circadian variation whereby postischemic forearm vascular resistance was higher (p<0.04) and postischemic forearm blood flow was lower (p<0.004) when responses in the morn-
ing (8 AM and night (9 PM) were compared with noon and 5 PM (Figure 1), a pattern similar to the observed variation in ischemic threshold.

There was a strong positive correlation between the postischemic forearm blood flow and the ischemic threshold during treadmill exercise ($p<0.0001$; coefficient, $-4.89$; SEM, $1.18$); similarly, there was a strong negative correlation between postischemic vascular resistance and ischemic threshold ($p<0.0002$) (Figures 3 and 4). Thus, at the time of day when ischemic threshold during exercise was lowest, postischemic forearm vascular resistance was highest and postischemic forearm blood flow was lowest, and vice versa (Figures 3 and 4).

**Ambulatory ST Segment Monitoring**

Twenty-eight of 31 patients studied had transient episodes of ST segment depression during ambulatory monitoring; 88% of episodes were silent. Figure 5 demonstrates the circadian pattern of distribution of episodes of ST segment depression and the mean hourly heart rate during the 24-hour period in these patients.

The number of ischemic episodes reached a peak around 7 AM, whereas the mean heart rate began to increase at this time and reached a peak 2 hours later. Episodes were least likely to occur between 7 PM and 7 AM (7.4±5) compared with 20±3 episodes ($p<0.001$) between 7 AM and 7 PM.

**Discussion**

In stable coronary artery disease, there is a circadian pattern in the occurrence of transient ischemic episodes, with episodes being most frequent in the morning hours.$^{1-4}$ Heart rate, blood pressure, and probably also contractility are increased in the morning hours,$^{4,8,9}$ suggesting that increase in myocardial oxygen demand contributes importantly to the increased prevalence of ischemia in the morning.

In this study, we wished to examine whether changes in coronary vascular tone contributed to the increased morning incidence of ischemic events. Our hypothesis was that if vascular resistance changes were contributing to the observed changes in event rate, then coronary vascular resistance would be higher in the morning hours. Because coronary vascular resistance cannot be measured directly several times a day, we measured the consequences of alteration in ischemia-induced coronary vascular resistance by measuring the ischemic

*Figure 3.* Graphs show relation between ischemic threshold and postischemic forearm vascular resistance in two patients at different times of the day. Dep., depression.

*Figure 4.* Graph shows relation between ischemic threshold and postischemic forearm vascular resistance measured at four different times of the day in group A patients. Ischemic threshold is plotted at times of maximal, submaximal, subminimal, and minimal forearm vascular resistance irrespective of time of day. Results expressed as mean±SEM. bpm, Beats per minute.

*Figure 5.* Graph shows hourly variation in transient episodes of ST segment depression and mean hourly heart rate. bpm, Beats per minute.
threshold during exercise. Thus, if the lowest coronary vascular resistance were to increase, one would expect a decreased ischemic threshold—that is, a lower heart rate or heart rate–blood pressure product at the development of 1-mm ST depression, and vice versa.

Our investigation demonstrated that the ischemic threshold in individual patients varied at different times of the day, suggesting that the coronary vascular resistance achieved during myocardial ischemia was subject to change. Furthermore, in the group as a whole, the ischemic threshold was lower in the morning and at night compared with other times of the day (Figure 1), implying similar and inverse changes in coronary vascular resistance during myocardial ischemia. These findings are supported by studies demonstrating narrower coronary arteries in the morning compared with the afternoon. Acute and chronic ischemic events are more prevalent in the few hours after awakening, a time of day when vascular resistance is also increased as shown in our study, in which the 8 AM test was performed within an hour of awakening. The increased coronary tone in the morning may also increase shear stress over a vulnerable atherosclerotic plaque, which may then become more prone to rupture with precipitation of an acute cardiac event at this time of the day.

Another important finding in our study was the presence of a very strong link between the ischemic threshold and forearm vascular resistance at different times of the day (Figures 3 and 4), suggesting that the changes in the lowest coronary resistance achieved during ischemia (derived from measurement of ischemic threshold) paralleled similar changes in forearm vascular resistance during forearm ischemia. The concurrent changes in posts ischemic forearm vascular resistance and ischemic threshold not only add weight to the hypothesis that there is a circadian variation in coronary vascular resistance during myocardial ischemia, but also suggest that factors altering coronary vascular resistance at different times of the day are unlikely to be local. Thus, they are likely to be the result of generalized changes in either humoral or neural mediators of vasomotor tone.

Several factors that affect vascular tone have a well-established circadian pattern of variation. For example, humoral vasoconstrictors norepinephrine and renin are higher in the morning compared with other times of the day. Plasma viscosity and platelet aggregability increase significantly in the morning; the increased tendency for platelets to aggregate in the morning may cause release of vasoconstrictors and result in increased vascular tone. Increase in neural sympathetic tone in the morning hours may cause increased stimulation of α-sympathetic receptors and lead to coronary and peripheral vasoconstriction. Whether one or a combination of these vasoconstrictor influences are responsible for the observed circadian change in vascular resistance is not clear and needs to be determined by further investigation.

Although ischemia is commonly believed to cause maximal relaxation of the resistance vasculature, our finding of a 40% variation in posts ischemic forearm vascular resistance at different times of the day illustrates that ischemia cannot override all constrictor influences and cause maximal dilation of resistance vessels. Because it is unlikely that our patients had stenotic lesions of their brachial arteries (none had any symptoms or physical findings involving reduced blood supply to the forearm), changes in posts ischemic resistance during the course of the day are likely to be largely if not entirely due to variation in the tone of the resistance vasculature or of the small prearteriolar vessels. A similar variation in ischemic threshold, and presumably of coronary vascular resistance during ischemia, suggests that myocardial ischemia also cannot override all constrictor influences and cause coronary resistance to fall to minimal levels. It is not known whether the factors responsible for causing this variation are acting primarily on the epicardial coronary arteries and influencing lesion diameter or, as in the forearm, affecting the resistance vasculature or small prearteriolar vessels. Elucidation of these factors and their site of action could be important in altering the increased occurrence of cardiac events in the morning.

The observation that ischemic threshold and forearm resistance have a secondary increase at night is of interest. Some studies have demonstrated a second rise in the frequency of transient ischemic episodes and myocardial infarction in the late evening (6–8 PM), and others have demonstrated a lowered ischemic threshold at night. The impact of these findings on the timing of clinical events is of interest: In the morning hours, ischemic threshold is low, presumably reflecting elevated coronary vascular resistance; this probably contributes to the morning peak in episodes of transient ischemia and perhaps also to the increased frequency of myocardial infarction and cardiac death at this time. As seen in Figure 5, the mean heart rate in patients undergoing ambulatory monitoring was lower at 8 AM (72±1 beats per minute) compared with noon (78±1 beats per minute); however, the peak in episodes of ischemia was reached at 8 AM, a time when coronary vascular resistance is presumably high. With increase in mean heart rate between 8 AM and noon, there is no further increase in frequency of ischemia possibly because of a decrease in coronary vascular tone (Figure 1). At night, ischemic threshold falls a second time, presumably again reflecting an increase in coronary vascular tone. Although this change would increase the tendency for ischemia to occur, it would be attenuated by the lower heart rate, blood pressure, and catecholamine levels present at this time of day. These concepts are supported by the demonstration of a lower heart rate–ischemic threshold during spontaneously occurring episodes of ischemia at night and in the early morning.

In group A patients who underwent four exercise tests, ischemic threshold was measured as the heart rate at the development of 1-mm ST segment depression. An intra-arterial line was not used to avoid interference with normal daily patterns of life. The finding of a lower heart rate at the onset of ischemia suggested a lower ischemic threshold. However, this occurred at a time when minimal peripheral vascular resistance (measured as posts ischemic forearm vascular resistance) was higher, which raises the question as to whether the blood pressure at these times was also higher. To overcome this concern, we performed a second study in group B patients in whom blood pressure could be measured continuously and accurately using an intra-arterial line. The exercise was performed in the morning and at 1 PM, times when the ischemic threshold determined by heart
rate alone was found to be lowest and highest, respectively. This second study demonstrated that the rate-pressure product was lower in the mornings and higher at 1 PM, which indicates that there is truly a circadian variation in ischemic threshold and, most likely, in coronary vascular tone.

Previous studies have examined the reproducibility of hemodynamic measurements and markers of ischemia in patients undergoing multiple exercise tests. The results have been variable; whereas some have reported a difference in these parameters, others have observed no significant changes. In this study, care was taken to ensure that we measured ischemic threshold by precipitating myocardial ischemia using an identical stimulus (treadmill exercise) at different times of the day. As observed in previous studies, patients had a variation in several parameters: the rate–pressure product at rest, the rate of increase in rate–pressure product with exercise, the duration of exercise to development of 1-mm ST segment depression, and the duration to peak exercise. The purpose of our study was to obtain an index of coronary tone at the time of an equivalent amount of myocardial ischemia at different times of the day. To this end, we believe that the measurement of rate–pressure product at the onset of 1-mm ST depression most closely reflects the lowest level of coronary vascular resistance even though it may have taken patients a variable amount of exercise to achieve this threshold at different times of the day.

Critique

In this study, we measured postischemic forearm vascular resistance after 5 minutes of forearm ischemia and measured ischemic threshold after 1-mm ST depression as an index of postischemic coronary vascular resistance. It is known that forearm blood flow occlusion of >5 minutes can further reduce forearm vascular resistance, and it is possible that greater degrees of myocardial ischemia may provoke further reductions in coronary vascular resistance. A more severe ischemic vasculature may or may not be subject to circadian changes. However, the purpose of this study was to determine whether coronary vasodilation produced by myocardial ischemia during daily activities is subject to vasomotor stimuli that could alter the ischemic threshold and thereby influence the ease with which ischemia can be precipitated at certain times of the day.

We have postulated that the lower rate–pressure product at ischemia in the morning is a reflection of higher coronary resistance at this time. However, it may also be caused by reduced extraction of oxygen into the myocardium in the mornings without any changes in coronary blood flow or by increase in contractility, and thus to increased myocardial oxygen demands in the morning.

Implications

This study demonstrates that the resistance of the coronary vasculature, even during myocardial ischemia, is subject to changes during the day. Factors responsible for these changes are likely to be generalized, as they also affect the forearm vasculature. The importance of increased α-sympathetic tone in determining the higher forearm vascular resistance in the mornings has recently been demonstrated.

The morning reduction in ischemic threshold probably contributes to the increased incidence of transient ischemic episodes in patients with coronary artery disease and may additionally contribute to the increased incidence of acute myocardial infarction and sudden cardiac death at this time. Identification of factors responsible for the observed circadian variation in vascular resistance may have important therapeutic implications regarding the use and efficacy of adrenergic receptor antagonists and vasodilators in reducing the increased morning incidence of adverse cardiac events.

References

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