JACC Vol. 27, No. 7
June 1996:1629–36

Patterns and Behavior of Transient Myocardial Ischemia in Stable Coronary Disease Are the Same in Both Men and Women: A Comparative Study

DAVID MULCAHY, MD, MRCPI, FESC, NADER DAKAK, MD, GLORIA ZALOS, RN, NEIL P. ANDREWS, MB, MRCP, MICHAEL PROSCHAN, PHD, MYRON A. WACLAWIW, PHD, WILLIAM H. SCHENKE, BA, ARSHED A. QUYYUMI, MD, MRCP, FACC

Bethesda, Maryland

Objectives. **This study sought to compare the circadian variations in transient ischemic activity, mean heart rate and ischemic threshold between women and men with coronary artery disease.**

Background. **There is a circadian variation in ischemic activity, onset of myocardial infarction and sudden cardiac death in patients with coronary artery disease, but studies assessing ischemia have incorporated predominantly male subjects.**

Methods. **Thirty-one women and 45 men underwent at least 48 h of ambulatory ST segment monitoring.**

Results. **There was a similar and significant circadian variation in ischemic activity in both women and men ($p < 0.0001$ and $p < 0.0001$, respectively), with a trough at night, a surge in the morning and a peak between 1 and 2 PM, corresponding to a similar circadian variation in mean hourly heart rate ($p < 0.0001$) that was not different between men and women ($p = 0.28$, power to detect a shift 99.9%). Mean heart rate at onset of ischemia (ischemic threshold) had similar variability in women and men ($p = 0.96$), and harmonic regression analysis confirmed a significant circadian variation ($p < 0.0001$), with a trough at night and a peak during activity hours. Heart rate increased significantly in the 5 min before ischemia throughout the 24 h ($p < 0.0001$), with no gender differences in the pattern of preonset to onset heart rate changes over time ($p = 0.52$); the smallest differences were recorded in the middle of the night. The majority of ischemic episodes (80%) had a heart rate increase >5 beats/min in the 5 min before ischemia, but there were no gender differences.**

Conclusions. **Women with coronary artery disease have a pattern of ischemic activity and underlying pathophysiologic mechanisms very similar to men. The importance of increase in myocardial oxygen demand in the genesis of ischemia in both men and women is reflected by similar magnitude of heart rate increases before ischemia. The lower ischemic threshold during the nocturnal hours, when blood pressure is also lower, is consistent with a circadian variation in underlying coronary vascular tone.**

(J Am Coll Cardiol 1996;27:1629–36)

Much interest has centered around circadian variations in various physiologic and pathophysiologic cardiovascular processes in recent years since it was reported that acute myocardial infarction was more likely to occur in the morning waking hours than at other times of the day (1–3). It is now known that the morning waking hours are associated with an increased incidence of sudden cardiac death (4, 5), ventricular arrhythmias (6) and ischemic stroke (7). Ischemic activity during the daily lives of patients with coronary disease mirrors the circadian patterns of acute cardiac events, with a surge in the morning waking hours, a plateau in the early afternoon, a possible secondary evening peak and a trough at night (8–10). Potentially pertinent to this circadian variation in ischemic activity are similar circadian variations in 1) the determinants of myocardial oxygen demand (heart rate and blood pressure) (11) and 2) sympathetic activity, plasma catecholamine levels (12) and plasma renin activity (13), all mediators of vasomotor tone.

Studies investigating various aspects of coronary artery disease have used subjects who were either entirely or predominantly men and then extrapolated the results to women. This is partly explained by the relative paucity of women with documented coronary artery disease in the past. However, the ratio of men to women with coronary artery disease is changing, and it is now a major cause of morbidity and mortality in women in the western world (14). Several local factors that impact on vessel biology, in particular on endothelial function, may vary between men and women. For example, it has recently been shown that estrogens may play an important role in determining endothelial function and thus vascular vasomotor tone (15–18). No study assessing ischemic activity during daily life and possible underlying mechanisms has focused on women with documented coronary disease to date. We undertook this study to assess variations in both transient ischemic

From the Cardiology Branch and Office of Biostatistics Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Manuscript received September 21, 1995; revised manuscript received January 5, 1996, accepted January 23, 1996.

Address for correspondence: Dr. Arshed A. Quyyumi, Cardiology Branch, Building 10 7B15, 10 Center Drive MSC 1650, National Institutes of Health, Bethesda, Maryland 20892.

0735-1097/96/$15.00
PII S0735-1097(96)00061-7

JACC Vol. 27, No. 7
June 1996:1629–36

activity and its underlying pathophysiologic mechanisms in predominantly postmenopausal women with documented coronary artery disease and compared these findings with a "control" group of men with documented coronary disease.

Methods

Patients. Female patients investigated in the Cardiology Branch of the National Heart Lung and Blood Institute who had documented native coronary artery disease (>50% lumen narrowing of at least one major vessel or its major branch) and had ischemic activity recorded during ambulatory ST segment monitoring constituted the study group. The patients are part of a study examining the natural history of transient ischemia in patients with coronary artery disease. Patients were monitored after withdrawal of all antianginal therapy for at least 48 h, although short-acting nitrates were available for pain. Exclusion criteria included the presence of significant conduction disturbances, use of medications likely to affect interpretation of the ST segment and prior coronary artery bypass surgery. Patients were advised to be active and maintain their normal daily schedules out of hospital during the monitoring period. A total of 31 women (45 to 78 years old, mean age 65) of the 87 who had undergone monitoring during this period fulfilled the inclusion criteria. Thus, episodes of ST segment depression occurred in 36% of the women screened. Monitoring was performed either at the time of initial investigation or serially, including times of subsequent outpatient visits when medications were also routinely withdrawn. Thirty patients had reached the menopause by the time of inclusion in the study, and 12 had undergone previous hysterectomy and/or oophorectomy. Seven patients had taken hormone replacement therapy for short periods of time several years before the study, and two patients were receiving current treatment with premarin. A control group of age-matched male patients with coronary artery disease was assembled such that there would be twice as many ischemic episodes recorded during ambulatory monitoring available for analysis as from the women. A total of 45 men (44 to 83 years old, mean age 66) were included. Five women and four men had previously undergone coronary angioplasty, all >2 years before ambulatory monitoring. Postprocedural angiography in all patients confirmed significant persistent stenosis either in the angioplasty vessel or at another site.

Ambulatory ST segment monitoring. Patients underwent ambulatory ST segment monitoring for 48 h during unrestricted normal daily activities. After careful skin preparation, bipolar leads CM_5 and modified lead 11 were monitored, as previously described (19). Initial recordings were made in different positions. Tapes were analyzed visually and automatically at 120 times normal speed, using the Delmar Avionics model 750A system. Real-time printouts at a paper speed of 25 mm/s were obtained before, at the onset, during and at the end of episodes of ST segment change. An ischemic episode was defined as >1 mm ST segment depression, either planar or downsloping, occurring 0.08 s after the J point and lasting >1 min. Return of the ST segment to baseline for at least 3 min was required between two episodes. Changes in T wave configuration alone were not considered significant for ischemia.

Each ischemic episode was documented for time of onset. The ischemic threshold was defined as the heart rate at the point where the ST segment began to depress on the corresponding ST segment trend. As described previously, the early manifestation of repolarization abnormality was obvious when the ST segment shift was 0.25 mm, but only episodes where the maximal depression reached ≤1 mm were included in the analysis (19). Also recorded from the heart rate and ST segment trends in each case was the heart rate ~5 min before the onset of ST segment depression. Mean hourly heart rates were also documented for 24-h tapes. All ischemic episodes were confirmed by real-time printouts, and the ischemic threshold and the heart rate 5 min before each ischemic episode were derived from the ST segment and heart rate trends.

Statistical analysis. Statistical analyses were chosen to address the following questions: 1) Are ischemic events uniformly distributed throughout the day, or is there a circadian pattern to the data? 2) Is there a circadian pattern to mean hourly heart rate, and is it the same for women and men? 3) Is there a circadian pattern to heart rate at onset of ischemia (ischemic threshold), and is this the same for women and men? 4) Is there a significant increase in heart rate before the onset of ischemia, and does this increase depend on gender or time of onset, or both?

Circadian pattern of ischemic activity was addressed by comparing the numbers of events in each of the four 6-h periods midnight to 6 AM, 6 AM to noon, noon to 6 PM and 6 PM to midnight. A specific permutation test that preserved the correlation structure of the data was used. Separate tests were performed for all patients combined and for women and men separately.

Circadian pattern of mean hourly heart rate was investigated using harmonic regression. For each patient, mean hourly heart rate was computed, and a harmonic regression equation with two harmonics was calculated, expressing the relationship of mean heart rate and time of day for that patient. The regression equation specified that the mean heart rate during the hour with midpoint t (time 0 is taken to be midnight, so t = 0.5 is half-past midnight; and t = 23.5 is 11.30 PM) is $\beta_0 + \beta_1 \cos(2\pi t/24) + \beta_2 \sin(2\pi t/24) + \beta_3 \cos(4\pi t/24) + \beta_4 \sin(4\pi t/24)$. The first cosine and sine pair represent the first harmonic. Using only the first harmonic allows only a single peak heart rate period. The second sine and cosine pair represent the second harmonic, allowing the possibility of a second peak heart rate period and a better fit to the data. A regression equation for the entire group (and for the sexes) was obtained by averaging the coefficients of individual patient's regression equations.

The analysis of *circadian pattern of heart rate at onset of ischemia (ischemic threshold)* was performed using the same harmonic regression approach as above. Unlike mean hourly

heart rate, a patient might have ischemia (and therefore contribute data) in only 1 h. Because of this and dependence among multiple measurements on the same patient, the generalized estimating equation approach (20) was used to obtain estimates of standard error. This was carried out separately for women and men.

Heart rate increases before ischemia were assessed using harmonic regression and the generalized estimating equation. The dependent variable was the difference between the onset heart rate (ischemic threshold) and heart rate 5 min before onset for each episode; the independent variables were the two harmonics alluded to previously. Separate regressions were run for women and men. In each of the last three questions, circadian patterns in women were compared to those in men by simultaneously testing whether all sine and cosine coefficients were the same for the two sexes. The circadian pattern of mean heart rate was performed using Hotelling's T^2 test (21), whereas for ischemic threshold and heart rate before ischemia, quadratic-form chi-squared tests were performed. In the absence of a significant difference, a single equation allowing women and men to differ only in intercept was constructed.

Differences between means were tested using the two-tailed Student *t* test for continuous variables and using the chi-square test for discrete variables. A p value <0.05 was considered significant.

Results

A total of 76 patients (31 women, 45 men) with documented coronary artery disease (26 with single-vessel, 27 with two-vessel and 23 with three-vessel disease) and stable symptoms were included. The severity of coronary artery disease was greater in men than in women, with the frequency of three-vessel disease being greater and of single-vessel disease lower in men than in women (Table 1). There were no significant differences between men and women regarding age, rest or exercise left ventricular function or the incidence of diabetes, hypertension or previous myocardial infarction. Cholesterol level was higher in women (Table 1). Ninety percent of women and all men had ST segment depression during treadmill exercise testing. Two of the three women without ST depression had performed inadequate exercise tests. The heart rate at the onset of ST depression in men tended to be lower compared to women, but the difference did not reach statistical significance ($p = 0.1$, Table 1).

A total of 1,009 transient ischemic episodes (340 in women; 669 in men) were documented during 320 days (total 7,662 h) of monitoring: 340 in 107 days in women and 669 in 213 days in men. A further 112 twenty-four-hour tapes (52 in women, 60 in men) comprising 2,676 h recorded in these patients were negative for any ischemic changes. The recordings were complete for 99% of all the 24-h periods in both men and women. Most Holter monitors were removed during the morning hours, but the maximal loss of recording in any hour of the day did not exceed 3% of all the hours recorded in the cohort studied.

Table 1. Patient Characteristics

	Women (n = 31)	Men (n = 45)	p Value
Age (yr)	60 ± 7	61 ± 7	
Cholesterol (mg/dl)	263 ± 48	253 ± 51	< 0.02
Diabetes	5 (16%)	6 (13%)	
Hypertension	19 (61%)	17 (38%)	
Rest LVEF (%)	54 ± 15	54 ± 10	
Exercise LVEF (%)	49 ± 15	52 ± 10	
LVEF <45%	8 (26%)	7 (16%)	
Previous Q wave MI	5 (16%)	10 (22%)	
Severity of CAD			
1 VD	18 (58%)	8 (18%)	< 0.001
2 VD	8 (26%)	19 (42%)	
3 VD	5 (16%)	18 (40%)	< 0.05
Treadmill exercise			
HR at ST depression onset (beats/min)	120.5 ± 20	114.5 ± 15	
Peak HR (beats/min)	135 ± 24	135 ± 21	
Positive test	28 (90%)	45 (100%)	
Pain during test	16 (52%)	23 (51%)	
Medications			
Beta-receptor antagonists	9 (29%)	15 (33%)	
Calcium anatgonists	24 (77%)	27 (60%)	
Nitrates	15 (48%)	9 (20%)	< 0.02

Data presented are mean value ± SD or number (%) of patients. CAD = coronary artery disease; HR = heart rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; VD = vessel disease.

Circadian pattern of ischemia, ischemic threshold and hourly heart rate. The circadian variation in transient ischemia, heart rate at onset of ischemia (ischemic threshold) and mean hourly heart rate for the total group (n = 76) were similar, with a trough at night (midnight to 6 AM), a surge in the morning waking hours and a plateau during the day. Of the 1,009 ischemic episodes recorded, 62 (6.2%) occurred between midnight and 6 AM, 337 (33.3%) between 6 AM and noon, 346 (34.2%) between noon and 6 PM and 264 (26.3%) between 6 PM and midnight ($p < 0.0001$). Mean heart rate at onset of ischemia (ischemic threshold) was 82.1, 93.1, 93.8 and 89.9 beats/min, respectively, for the four 6-h time periods. Harmonic regression analysis was significant ($p < 0.0001$). A similar pattern of circadian variation was also noted in the mean hourly heart rate ($p < 0.0001$).

Comparison of women and men. Figure 1 assesses women and men separately and shows circadian patterns of ischemia, heart rate at onset of ischemia (ischemic threshold) and mean hourly heart rate between the sexes. There was a similar circadian variation in ischemic activity in both sexes ($p < 0.0001$ for each sex), and by far the fewest episodes occurred between midnight and 6 AM in both groups (6.7% vs. 5.8% of total ischemic episodes for women and men). Mean hourly heart rate was somewhat higher in women ($p < 0.04$ for comparison of intercepts), but there was no difference in heart rate pattern over time ($p = 0.28$ for simultaneous comparison of coefficients other than the intercept). This lack of signifi-

JACC Vol. 27, No. 7
June 1996:1629–36

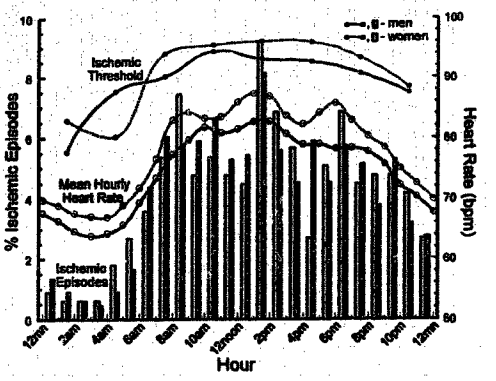

Figure 1. Circadian variation of transient myocardial ischemia (**vertical bars**), ischemic threshold (**solid circles**) and mean hourly heart rate (**open circles**) in women (**open bars, dotted lines**) and men (**solid bars, solid lines**) with coronary artery disease. bpm = beats per minute; mn = midnight.

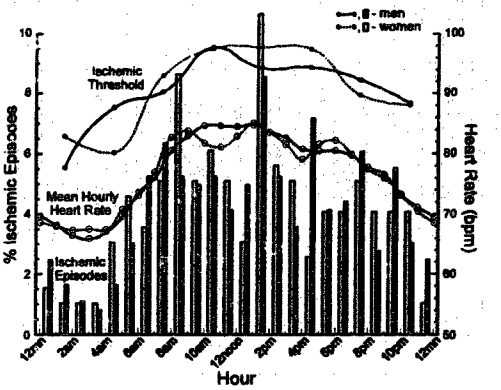

Figure 2. Circadian variation of transient myocardial ischemia (**vertical bars**), ischemic threshold (**solid circles**) and mean hourly heart rate (**open circles**) in women (**open bars, dotted lines**) and men (**solid bars, solid lines**) with episodes of ischemia during the nocturnal hours (midnight to 6 AM) in addition to other times of the day. Abbreviations as in Figure 1.

cance occurred in spite of the fact that the power to detect a 2-h shift in the male curve relative to the female curve was 99.9%. Both harmonics were significant ($p < 0.0001$ for each harmonic), indicating a definite circadian pattern of mean hourly heart rate over time. The lowest mean hourly heart rates occurred between 3 and 4 AM, and the highest just after noon, a period when the peak in ischemic activity for both sexes was also recorded.

Harmonic regression analysis showed no significant difference between the sexes in the pattern of heart rate at onset of ischemia (ischemic threshold) over time ($p = 0.96$ for simultaneous comparison of regression coefficients other than intercept). Both harmonics were significant ($p < 0.0001$ for each harmonic); as for the total group, the circadian patterns of heart rate at onset of ischemia (ischemic threshold) were very similar to those of mean hourly heart rate.

Comparison of the daytime period (6 AM to 10 PM) and the nighttime period (10 PM to 6 AM) showed a similar distribution in the number of episodes, and heart rate at the onset of ischemia between women and men (daytime: women, ischemic episodes 87.7%, heart rate at onset ischemia 94.6 beats/min; men, ischemic episodes 88.2%, heart rate at onset ischemia 92.0 beats/min. Nighttime: women, ischemic episodes 12.3%, heart rate at onset ischemia 84.2 beats/min; men, ischemic episodes 11.8%, heart rate at onset ischemia 84.8 beats/min).

Patients with nocturnal ischemia. To examine whether patients with nocturnal ischemia had a different circadian distribution of these parameters than those with ischemia only during the day, we assessed the distribution of ischemic episodes, heart rate at onset of ischemia (ischemic threshold) and mean hourly heart rate in all women ($n = 13$) and men ($n = 20$) who had at least one ischemic episode recorded during the nocturnal hours (midnight to 6 AM) in addition to other times of the day (total 566 ischemic episodes; women $n = 198$; men $n = 368$) (Fig. 2). There was a similar circadian variation for both sexes in ischemic activity, ischemic threshold and mean hourly heart rate when compared with those of the total group.

Patients with three-vessel disease. Because more men had three-vessel disease than women, and the ischemic threshold during exercise is lower and the frequency of ambulant ischemia is greater in patients with more severe disease, we also analyzed the circadian distribution of ischemic episodes in the 23 patients (5 women, 18 men) with three-vessel disease. The distribution of ischemic episodes during the day was similar to that in the rest of the cohort studied: 9.6% of episodes between midnight and 6 AM, 30.8% between 6 AM and noon, 32.7% between noon and 6 PM and 26.9% between 6 PM and midnight.

Heart rate changes before ischemia. Figure 3 details the circadian pattern of heart rate at onset of ischemia (ischemic threshold) and heart rate 5 min before onset of ischemia for both sexes. Harmonic regression analysis confirmed no significant differences in the pattern of preonset to onset heart rate changes over either time ($p = 0.52$) or between the sexes ($p = 0.36$). Both harmonics were significant ($p < 0.0001$, respectively, for the first and second harmonics).

The circadian pattern of heart rate increase before ischemia was somewhat different from that of mean hourly heart rate and heart rate at onset of ischemia (ischemic threshold), the smallest differences between the heart rate 5 min before onset and onset heart rates being recorded in the middle of the night, and the greatest differences being recorded at around 8 AM. Of the 981 (97%) transient ischemic episodes recorded in which both the 5-min preonset and onset heart rates were analyzable, only 194 (20%) episodes were associated with a heart rate increase <5 beats/min in the 5 min preceding ischemia. These episodes were distributed equally between women (20.4%) and men (18.5%).

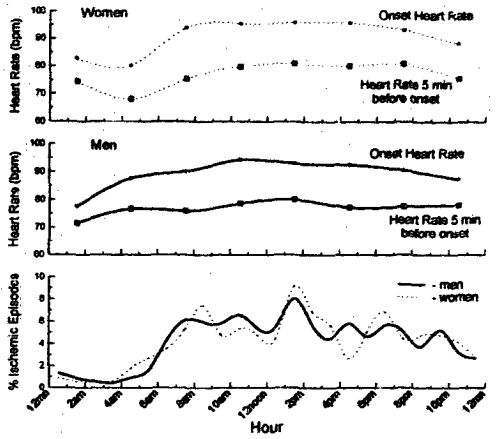

Figure 3. Relation of heart rate 5 min before ischemia onset (**squares**) and heart rate at onset of ischemia (ischemic threshold) (**circles**) on a 3-h basis in women (**dotted lines**) and men (**solid lines**) and corresponding 24-h patterns of ischemic activity in both men and women. Abbreviations as in Figure 1.

Discussion

Circadian variation of transient ischemia in women. Little has been published on observed patterns of ischemic activity during daily life in women with coronary artery disease. With the increasing prevalence of coronary artery disease in women, a greater understanding of both the behavior of ischemia and its possible underlying pathophysiologic mechanisms needs to be acquired, rather than assuming that the study of male patients will give answers that can then be applied to women. This study of ambulatory ST segment monitoring in postmenopausal women with coronary artery disease confirms that a distinct circadian variation of transient myocardial ischemia exists, with a surge in the morning hours and a trough at night that corresponds very closely to that shown both for men in this study and for predominantly male groups in other reported studies (8–10).

Two preliminary reports (22,23) from a recent multicenter trial investigating the circadian pattern of ischemia in women have yielded conflicting results. In a preliminary analysis of the Atenolol Silent Ischemia Trial (ASIST) data base, Thadani et al. (22) reported on 27 women with 130 episodes of transient ischemia during ambulatory monitoring; the recorded peak in ischemic activity was between 6 and 9 AM, with a trough at night. A follow-up abstract by Deedwania et al. (23) using the same data base included 40 women with transient ischemia. They concluded that women did not have a peak in ischemic activity in the morning waking hours but had two primary peaks at 4 AM and 12 noon and a secondary peak at 9 PM. The women included in that data base did not all have documented coronary artery disease. In contrast, in our study, we analyzed a threefold higher number of episodes and chose to include only patients with documented coronary disease, as false-positive ST segment depression is particularly prevalent in women with chest pain syndromes (24,25).

Circadian variation of myocardial infarction and sudden cardiac death in women. Willich et al. (4), in assessing the circadian variation in the incidence of sudden cardiac death in the Framingham heart study population, noted the increased propensity for both women and men to suffer sudden death in the morning waking hours and reported no difference in the overall circadian variation of sudden death between the sexes. Tofler et al. (3) reported almost identical circadian variations in onset of acute myocardial infarction for both sexes in an analysis of the Thrombolysis in Myocardial Infarction (TIMI) II study group. Whereas 15.1% of acute myocardial infarctions occurred between midnight and 6 AM in women, 34.2% occurred between 6 AM and 12 noon. Corresponding figures for men were 15.5% and 34.4%, respectively. Our results demonstrate that women with coronary artery disease also appear more likely to have ischemia predominantly in the morning waking hours and during the day, a distribution similar to the onset of acute myocardial infarction and sudden cardiac death reported previously (3,4).

Pathophysiologic considerations. *Increases in myocardial oxygen demand.* It has been demonstrated that the majority of transient ischemic episodes are preceded by an increase in heart rate and blood pressure (19,26–28) and that ischemic episodes rarely occur during daily life in those with a negative exercise test for ischemia (29), confirming the importance of increases in the determinants of myocardial oxygen demand in precipitating transient ischemic episodes.

This study confirms that the majority of transient ischemic episodes in both women and men with stable coronary artery disease are preceded by an increase in heart rate, and, moreover, the increase in heart rate from the mean to ischemia is similar throughout all periods of the day and night. The majority of ischemic episodes (80%) had an increase >5 beats/min in the 5-min period before onset of ST segment depression. A lack of substantial increase in heart rate before some ischemic episodes may be indicative of the importance of a primary reduction in coronary blood flow as a precipitating cause for ischemia. Alternatively, this may result from the fact that we chose the heart rate at 5 min before ischemia as the preonset measurement. Other studies have demonstrated that increases in heart rate may precede ischemia by up to 30 min (27), although the major increases occur in the immediate 5-min period before ischemia. The relation of activity to ischemia was clearly demonstrated recently by Parker et al. (30), who reported that when patients arose and commenced activities at 8 AM, there was a surge in heart rate and ischemic activity at this time. When the same patients did not arise and commence activities until midday on another day, the surge in heart rate and ischemic activity was delayed until afternoon. We did not have the time of awakening noted in all patient diaries, and it is possible that wake time adjustment of the variables measured and closer correlation with activities will yield important additional information.

JACC Vol. 27, No. 7
June 1996:1629–36

Decreases in myocardial oxygen supply. Because some episodes of ischemia occur at significantly lower heart rates in the same subjects, it has been postulated that alterations in coronary vasomotor tone, with resultant transient reductions in myocardial oxygen supply, might also contribute to the development of ischemic episodes (31). We and others have shown that the ischemic threshold is lower at night and early morning than during the rest of the day (10,32,33), suggesting that changes in coronary vasomotor tone may modulate ischemia.

Circadian variation in ischemic threshold. The present study shows that the heart rate at onset of ischemia (ischemic threshold) in both sexes is lower at night than during other periods of the day, suggesting that the coronary vascular resistance is higher at this time of the day. This observation is consistent with a previous study investigating circadian variation in ischemic threshold that used multiple exercise tests in patients with coronary artery disease (32). In that investigation, heart rate at onset of ischemia was lower in the early morning and late evening than at midday and late afternoon. This was accompanied by a simultaneous increase in forearm vascular resistance at these times. Taken together, these studies indicate that coronary vascular resistance is higher during the night and early morning than during the day and that this increase in vascular resistance is not simply localized to the coronary circulation. The finding of a lower ischemic threshold at night was also corroborated by Figueras et al. (33), using atrial pacing in patients with rest angina, and by Benhorin et al. (10), who, in a recent study of ambulatory ST segment monitoring in predominantly male patients with stable coronary disease, reported that the threshold of myocardial ischemia was lowest between 1 AM and 3 AM and highest between 10 AM and 1 PM.

To overcome the concern that patients with ischemic episodes occurring only during the day (at a higher ischemic threshold) may artificially produce a circadian variation in ischemic threshold, the subgroup of patients who had ischemic episodes both during the nighttime hours (midnight to 6 AM) in addition to other times of the day were analyzed, and this showed no difference in patterns of ischemia or in the variation in ischemic threshold for either women or men when compared to the overall group. We also showed that, within patients, ischemic episodes may occur at varying heart rate levels, although some increase in heart rate occurs before ischemia in most instances.

To exclude the possibility that patients with three-vessel disease, the majority of whom were men, may have a distinct and different distribution than the remaining patients, we analyzed their episodes separately and showed that there was no difference in the circadian pattern in this subset of patients.

Mechanisms of nocturnal ischemia. Our results indicate that the ischemic threshold is highest at a time when ischemic activity is greatest, suggesting that increases in myocardial oxygen demand play a crucial role in the generation of ischemia during activity hours. The mechanisms for a reduction in the ischemic threshold at night are not clear, and it is somewhat surprising that the trough in ischemic activity corresponds with a trough in ischemic threshold, an observation

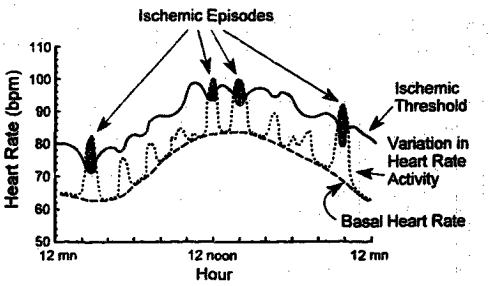

Figure 4. Proposed pattern and mechanisms of ischemia, showing circadian variation in basal heart rate, heart rate at onset of ischemia (ischemic threshold) and transient ischemic activity during both nocturnal and daytime hours. Both rest heart rate and the ischemic threshold are variable but reach a trough at night, and during the day both rest heart rate and the ischemic threshold are variable but significantly higher. The relative increases from basal heart rate levels required to reach the ischemic threshold are similar during the 24 h; however, during the activity period, the ischemic threshold is much more likely to be reached despite the fact that it is higher than at night. Abbreviations as in Figure 1.

that has, however, been noted when assessing the effects of beta-blocking agents on ischemic activity during exercise and daily life (34): These agents classically reduce the frequency of ischemic activity, but persisting ischemia tends to occur at a lower onset heart rate. However, because there is evidence for a generalized increase in vasomotor tone at night and in the early morning, it is likely that changes in systemic neurohumoral activity play an important role.

Increases in ventricular volumes in the supine position may lead to increases in wall tension and end-diastolic pressure so that lesser increases in heart rate result in myocardial ischemia. It has been shown that increases in heart rate precede the majority of nocturnal ischemic episodes. Sleep studies have demonstrated that such increases in heart rate were caused by arousal and occasionally by REM sleep (35), and Barry et al. (36) have reported that the majority of nocturnal episodes occurred in association with some activity, such as rising to micturate. Thus, the relative lack of ischemic episodes at night in most patients appears to result from a lack of any increases in myocardial oxygen demand sufficient to cause ischemia even in the presence of an apparent increase in coronary vasoconstrictor tone. In contrast, during the day, there are many episodes during which increases in heart rate, resulting from physical or mental stress, exceed the ischemic threshold, despite the fact that coronary vasomotor tone is lower and the ischemic threshold is significantly higher. It is also possible that vasodilators that counteract coronary vasoconstrictor tone may be of special benefit in patients with nocturnal ischemic episodes.

Proposed mechanisms for transient ischemia. On the basis of the findings of this and other studies, Figure 4 illustrates potential mechanisms at play in the genesis of transient myocardial ischemia in women and men with stable coronary

artery disease. The ischemic threshold is reached at a lower level at night than during the day, supporting a circadian variation in coronary vasomotor tone, which is increased at night. The mean hourly heart rate (presumably mirroring mean basal hourly heart rate) also has a very similar circadian variation, with a trough at night, and thus the relative increase in heart rate required to produce ischemia is similar at nighttime compared with all other times of the day. This underscores the importance of heart rate increases in the genesis of ischemia throughout the 24-h period, even allowing for variations in coronary tone.

There are no differences between women and men with stable coronary artery disease with regard to the timing of ischemia or its potential underlying pathophysiologic mechanisms. Both have distinct and similar circadian patterns of myocardial ischemia in association with similar circadian variations in ischemic threshold. A greater understanding of both the distribution of ischemic activity and the underlying pathophysiologic mechanisms in women with coronary artery disease is important both in assisting our increased awareness of coronary disease in women and from the therapeutic viewpoint. Although the women reported in this study are predominantly postmenopausal and cannot be assumed to have the same patterns of ischemic activity as those in the premenopausal stage, postmenopausal women represent the large majority of women with overt coronary artery disease worldwide. From the therapeutic viewpoint, the concept of 24-h protection with, in particular, cover for the surge in ischemic activity in the morning waking hours is applicable to women as well as men with confirmed coronary artery disease. Healy (37), referring to the "Yentl syndrome," reported that once a woman showed that she was just like a man by having a myocardial infarction, she was treated as a man would be. With regard to transient myocardial ischemia, this study confirms that the approach to the management of transient ischemia in stable coronary disease should be the same in both sexes.

References

1. Muller JE, Stone PH, Turi ZG, et al, and the MILIS Study Group. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–22.
2. Hjalmarson A, Gilpin EA, Nicod P, et al. Differing circadian patterns of symptom onset in subgroups of patients with myocardial infarction. Circulation 1989;80:267–75.
3. Tofler GH, Muller JE, Stone PH, et al. Modifiers of timing and possible triggers of acute myocardial infarction in the thrombolysis in myocardial infarction phase II (TIMI 11) Study Group. J Am Coll Cardiol 1992;20: 1049–55.
4. Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. Am J Cardiol 1987;60:801–8.
5. Willich SN, Goldberg RJ, Maclure M, Perriello L, Muller JE. Increased onset of sudden cardiac death in the first 3 h after awaking. Am J Cardiol 1992;70:65–8.
6. Lampert R, Rosenfeld L, Batsford W, Lee F, McPherson C. Circadian variation of sustained ventricular tachycardia in patients with coronary artery disease and implantible cardioverter-defibrillators. Circulation 1994;90: 241–7.
7. Marler JR, Price TR, Clark GL, et al. Morning increase in onset of ischemic stroke. Stroke 1989;20:472–6.
8. Rocco MB, Barry J, Campbell S, et al. Circadian variation of transient myocardial ischemia in patients with coronary artery disease. Circulation 1987;75:395–400.
9. Mulcahy D, Keegan J, Cunningham D, et al. Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. Lancet 1988;2: 755–9.
10. Benhorin J, Banai S, Moriel M, et al. Circadian variations in ischemic threshold and their relation to the occurrence of ischemic episodes. Circulation 1993;87:808–14.
11. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood pressure. Lancet 1978;1:795–7.
12. Tofler GH, Brezinski DA, Schafer AI, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987;316:1514–8.
13. Gordon RD, Wolfe LK, Island DP, Liddle GW. A diurnal rhythm in plasma renin activity in man. J Clin Invest 1966;45:1587–92.
14. Holdright D. Angina in women—assessment and management in the 1990s. Br J Cardiol 1994;1:323–31.
15. Hayashi T, Fukuto JM, Ignarro LJ, Chaudhuri G. Basal release of nitric oxide from aortic rings is greater in female rabbits than in male rabbits: implications for atherosclerosis. Proc Natl Acad Sci USA 1992;89:1159–63.
16. Chowienczyk PJ, Watts GF, Cockcroft JR, Brett SE, Ritter JM. Sex differences in endothelial function in normal and hypercholesterolemic subjects. Lancet 1994;2:305–6.
17. Gilligan DM, Quyyumi AA, Cannon RO. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. Circulation 1994;89:2545–51.
18. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO. Acute vascular effects of estrogen in postmenopausal women. Circulation 1994;90: 786–91.
19. Panza JA, Diodati JG, Callahan TS, Epstein SE, Quyyumi AA. Role of increases in heart rate in determining the occurrence and frequency of myocardial ischemia during daily life in patients with stable coronary artery disease. J Am Coll Cardiol 1992;20:1092–8.
20. Liang K, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrica 1986;73:13–22.
21. Afifi AA, Azen SP. Statistical Analysis: A Computer Oriented Approach. New York: Academic Press, 1979:285.
22. Thadani U, Hill JA, Cohn PF, et al, for the ASIST study group. Prevalence and frequency distribution of ambulant silent ischemia in asymptomatic and minimally symptomatic women with CAD [abstract]. Circulation 1992;86 Suppl I:H15.
23. Deedwania PC, Pepine C, Thadani U, Marks R, Handberg E, for the ASIST study group. Gender differences in circadian pattern of transient ischemic episodes in asymptomatic and minimally symptomatic patients with CAD [abstract]. J Am Coll Cardiol 1994;23:6A.
24. Cumming GR, Dufresne C, Kich L, Samm J. Exercise electrocardiogram patterns in normal women. Br Heart J 1973;35:1055–61.
25. Pratt CM, Francis MJ, Divine GW, Young JB. Exercise testing in women with chest pain: are there additional exercise characteristics that predict true positive test results? Chest 1989;95:139–44.
26. Deedwania PC, Nelson JR. Pathophysiology of silent myocardial ischemia during daily life: hemodynamic evaluation by simultaneous electrocardiographic and blood pressure monitoring. Circulation 1990;82:1296–304.
27. McLenachan JM, Weidinger FF, Barry J, et al. Relations between heart rate, ischemia, and drug therapy during daily life in patients with coronary artery disease. Circulation 1991;83:1263–70.
28. Andrews TC, Fenton T, Toyosaki N, et al. Subsets of ambulatory myocardial ischemia based on heart rate activity. Circadian distribution and response to anti-ischemic medication. Circulation 1993;88:92–100.
29. Mulcahy D, Keegan J, Sparrow J, Park A, Wright C, Fox KM. Ischemia in the ambulatory setting—the total ischemic burden: relation to exercise testing and investigative and therapeutic implications. J Am Coll Cardiol 1989;14:1166–72.
30. Parker JD, Testa MA, Jimenez AH, et al. Morning increase in ambulatory ischemia in patients with stable coronary artery disease. Importance of physical activity and increased cardiac demand. Circulation 1994;89:604–14.
31. Deanfield JE, Selwyn AP, Chierchia S, et al. Myocardial ischaemia during

daily life in patients with stable angina: its relation to symptoms and heart rate change. Lancet 1983;2:753–8.
32. Quyyumi AA, Panza JA, Diodati JG, Lakatos E, Epstein SE. Circadian variation in ischemic threshold. A mechanism underlying the circadian variation in ischemic events. Circulation 1992;86:22–8.
33. Figueras J, Cinca J, Balda F, Moya A, Rius J. Resting angina with fixed coronary artery stenosis. Nocturnal decline in ischemic threshold. Circulation 1986;74:1248–54.
34. Davies RF, Herbert M, Habibi H, et al, CASIS investigation. Beta-blockers lower the heart rate threshold for ischemia during ambulatory monitoring [abstract]. J Am Coll Cardiol 1993;21:20A.
35. Quyyumi AA, Efthimiou J, Quyyumi A, Mockus LJ, Spiro SG, Fox KM. Nocturnal angina: precipitating factors in patients with coronary artery disease and those with variant angina. Br Heart J 1985;56:346–52.
36. Barry J, Campbell S, Yeung AC, Raby KE, Selwyn AP. Waking and rising at night as a trigger of myocardial ischemia. Am J Cardiol 1991;67:1067–72.
37. Healy B. The Yentl syndrome. N Engl J Med 1991;325:274–6.