Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 38, No. 3, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01451-6

Changes in Heart Rate and Heart Rate Variability Before Ambulatory Ischemic Events

Willem J. Kop, PHD,*† Ralph J. Verdino, MD, FACC,†‡ John S. Gottdiener, MD, FACC,§ Shaun T. O'Leary, MD, PHD,‖ C. Noel Bairey Merz, MD, FACC,¶ David S. Krantz, PHD*

Bethesda, Maryland; Washington, DC; Philadelphia, Pennsylvania; Roslyn, New York; Detroit, Michigan; and Los Angeles, California

OBJECTIVES The aim of this study was to determine the time course of autonomic nervous system activity preceding ambulatory ischemic events.

BACKGROUND Vagal withdrawal can produce myocardial ischemia and may be involved in the genesis of ambulatory ischemic events. We analyzed trajectories of heart rate variability (HRV) 1 h before and after ischemic events, and we examined the role of exercise and mental stress in preischemic autonomic changes.

METHODS Male patients with stable coronary artery disease (n = 19; 62.1 ± 9.3 years) underwent 48-h ambulatory electrocardiographic monitoring. Frequency domain HRV measures were assessed for 60 min before and after each of 68 ischemic events and during nonischemic heart rate-matched control periods.

RESULTS High-frequency HRV decreased from −60, −20 to −10 min before ischemic events (4.8 ± 1.3; 4.6 ± 1.3; 4.4 ± 1.2 ln [ms^2], respectively; $p = 0.04$) and further from −4, −2 min, until ischemia (4.4 ± 1.3; 4.1 ± 1.3; 3.7 ± 1.2 ln [ms^2]; p's < 0.01). Low frequency HRV decreases started at −4 min ($p < 0.05$). Ischemic events occurring at high mental activities were preceded by depressed high frequency HRV levels compared with events at low mental activity ($p = 0.038$ at −4 min, $p = 0.045$ at −2 min), whereas the effects of mental activities were not observed during nonischemic control periods. Heart rate variability measures remained significantly decreased for 20 min after recovery of ST-segment depression when events were triggered by high activity levels.

CONCLUSIONS Autonomic changes consistent with vagal withdrawal can act as a precipitating factor for daily life ischemia, particularly in episodes triggered by mental activities. (J Am Coll Cardiol 2001; 38:742–9) © 2001 by the American College of Cardiology

Transient myocardial ischemia and sudden cardiac death are often preceded by periods of changes in autonomic nervous system activity consistent with vagal withdrawal (1). Depressed levels of heart rate variability (HRV) also predict future cardiac morbidity and mortality in patients with coronary artery disease, congestive heart failure and valvular heart disease (2–4). Possible pathophysiologic mechanisms linking autonomic changes to adverse outcomes include vagally mediated increases in cardiac demand (5–8) and reduced coronary blood supply due to coronary constriction (9).

Physical exercise and mental stress are potent triggers of myocardial ischemia (10–13). The neural mechanisms for mental stress-induced ischemia are not well understood but are likely to involve both the parasympathetic (14,15) and sympathetic (16,17) nervous systems. Physical and mental challenges provoke transient decreases in the high-frequency component of HRV (6,16). This study investigates the time course of autonomic changes before ambulatory ischemia and determines the effects of mental and physical activities on preischemic autonomic changes.

Spectral analysis of HRV has been used to document changes in sympathetic/parasympathetic balance. Research has demonstrated that the high-frequency component of HRV primarily reflects vagal tone (18); the low-frequency component of HRV and the ratio of the low- and high-frequency components have been proposed as indicators of sympathetic/parasympathetic balance (19,20), although most evidence appears to be inconsistent with this notion (21). Transient variations in HRV have recently been validated as a measure of short-term changes in autonomic tone (22,23). To investigate the role of autonomic changes in the onset of ischemic events, we examined whether indicators of decreased vagal tone precede ischemic events documented by ambulatory electrocardiography. We further compared preischemic autonomic changes during episodes of high versus low physical and mental activities during daily life.

From the *Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences Bethesda, Bethesda, Maryland; †Division of Cardiology, Department of Medicine, Georgetown University Medical Center Washington, DC; ‡Division of Cardiology, University of Pennsylvania, Philadelphia, Pennsylvania; §Noninvasive Cardiology, Saint Francis Hospital, Roslyn, New York; ‖Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan; and the ¶Division of Cardiology, Department of Medicine, Cedar Sinai Research Institute, Los Angeles, California. Supported by grants from the NIH (HL58638, HL47337), Safe-a-Heart Foundation (Los Angeles, California) and the Charles E. Dana Foundation. The opinions and assertions expressed herein are those of the authors and are not to be construed as reflecting the views of the USUHS or the US Department of Defense.

Manuscript received May 19, 2000; revised manuscript received May 7, 2001, accepted June 1, 2001.

Abbreviations and Acronyms

ANOVA = analysis of variance
ECG = electrocardiogram
HRV = heart rate variability

METHODS

Patients. We studied 19 men (mean age 62.1 ± 9.3 years) with stable angina and coronary artery disease documented by previous angiography. All patients had a previous positive exercise test for myocardial ischemia and evidenced ischemia during 48-h ambulatory electrocardiographic (ECG) monitoring, as described below. The study was approved by the Institutional Review Boards of the study sites, and patients gave written informed consent.

Ambulatory ECG monitoring. Ambulatory ECG monitoring was performed while anti-ischemic medications (beta-adrenergic blocking agents, calcium antagonists and long-acting nitrates) were held for greater than three half lives. Patients were monitored for a total of 48 h as described previously (24,25). We and other laboratories have previously documented the within-patient reliability of these HRV assessments (23,26). A Cardiodata AM recorder (frequency response 0.05 Hz to 100 Hz) was used with ECG signal calibration at 1 mV = 10 mm, using two sets of bipolar leads (V_5 and a modified inferior position to monitor the lead with the greatest ST-segment depression noted during exercise testing). Ambulatory recordings were analyzed by two experienced readers using a Marquette 8000 Series Holter. Artifacts were removed by overreading the 48 h ECG recordings, and analyses included only ECGs in sinus rhythm with optimal data quality for detection of R waves.

ST-segment analysis of ambulatory ECG monitoring. Analyses were performed after each recording was completely edited and artifacts removed. An ischemic response was defined as horizontal or downsloping ST-segment depression of ≥1 mm below the isoelectric baseline, measured 80 ms after the J point and persisting for ≥60 s. Upsloping ST depression ≥1.5 mm was not observed. Electrocardiographic data were independently reviewed by two experienced investigators, and disagreements were settled by consensus.

For each episode of ST-segment depression, the time of onset, duration and magnitude were recorded. Heart rate was assessed at the following time points before and after ischemia: 1) before an ischemic event at 60 min, 20 min, 10 min, 4 min and 2 min; and 2) after the ischemic event (i.e., when ST-segment depression returned to baseline) at 2 min, 10 min, 20 min and 60 min. Data quality and omission of ectopic beats were determined for each these time periods. ST depression during sleep was not included in this analysis. To prevent potential redundancy in the data due to overlapping of successive ischemic events, multiple ischemic events were excluded if those occurred within a 20-min time frame. If successive events occurred in the 20- to 60-min time frame (9/68 events), then the 60-min data points were discarded.

HRV analysis. Heart rate variability was used as indicator of autonomic activity in accordance with guidelines for standardization (18,27). Heart rate variability was assessed 60, 20, 10, 4 and 2 min before each ischemic event and 2, 10, 20 and 60 min after ischemia. Heart rate variability was assessed using a Marquette series 8000 Holter system (Marquette Electronics, Inc., Milwaukee, Wisconsin) (26). To examine the time course of HRV before ischemic events, the system was programmed to divide the ECG recordings into 2 min intervals, and changes in HRV were assessed using the frequency domain parameters (27) using a semi-automatic software program (Marquette Heart Rate Variability Program 002A). Spectral analysis by Fast Fourier Transform to separate R-R intervals was used to determine high (0.15 to 0.40 Hz) and low (0.04 to 0.15 Hz) frequency bands. The power of each frequency band was logarithmically transformed to avoid undue influence of extreme values in parametric statistical analyses, and expressed in ln (ms^2). The low frequency/high frequency ratio was also calculated (18,27). Although prospective studies indicate predictive value of high frequency and particularly low-frequency HRV measures, the physiological underpinnings of the low-frequency HRV component and the low-/high-frequency ratio are not well understood (21).

Control periods matched for heart rate. Nonischemic control periods were identified to determine whether the preischemic changes in HRV components were specific to ischemic events or whether such decreases merely reflected fluctuations in heart rate. These control periods were selected based on the ischemic heart rate profile for each patient, with readers blinded to physical and mental activity levels. Specifically, heart rate was selected to be the same (±5 beats/min) as during the patient's ischemic event, and the heart rates at 20 min and 10 min before ischemia were required to be the same as well. Changes in HRV for control periods were analyzed at parallel time intervals as the ischemic events (i.e., 20, 10, 4 and 2 min before the control episode and 2, 10 and 20 min after control episode). Patients were not included in the heart rate-matched control analyses (n = 6/19) if heart rate trajectories that matched their preischemic heart rate trajectories could not be found.

Analysis of patient diaries for physical and mental activities. A validated diary system was used to evaluate patients' physical and mental activities throughout the day (24,25,28,29). As described previously (24,25), patients were carefully instructed how to complete a standardized page each time their activities changed markedly. Mental and physical activity levels coinciding with the onset of ischemia were graded on a scale from 1 to 6, as described previously (24). Examples of physical activity classifications are: 1) sleep; 2) rest, reclining; 3) talking, eating; 4) driving, dressing; 5) shopping, and 6) climbing stairs, heavy physical

work. Examples of mental activity classification are: 1) sleep; 2) rest, reading; 3) talking, clerical work; 4) waiting, driving; 5) concentrating; and 6) anger or anxiety. Cut-off points for activity levels were used to compare HRV trajectories occurring at low (scores <5) versus high (scores ≥5) activity levels (24,25). Patients also recorded episodes of chest pain and use of nitroglycerin. Activity levels were cross tabulated with the concurrent ischemic events as well as with the nonischemic control periods, and it was required that a valid activity entry was made that covered the 10-min period before onset of the ischemic event.

Statistical analyses. Data are presented as mean ± SD. The changes in high frequency and low frequency HRV were first analyzed across all time points before the ischemic event using repeated measures analyses of variance (ANOVA). Subsequently, paired *t* tests were used to compare time intervals only if the repeated measures ANOVA for change over time was statistically significant. Separate repeated measures ANOVA were performed to examine recovery patterns of HRV.

The effects of physical and mental activities were examined using mixed-model ANOVA, comparing high versus low activity levels as between subjects factor, repeated measures of HRV as within subject factor, and differences between high versus low activity levels in preischemic HRV trajectories were evaluated by examining the interaction term ("high vs. low activity" × "repeated HRV assessments"). To further examine at which time points activities were related to HRV measures, separate between group *t* tests were conducted using Holm's adjusted p values for familywise error as well as unadjusted p values. Associations between changes in heart rate and HRV were tested using product-moment correlations. To examine whether changes in HRV were independent of increases in heart rate before ischemic events, the time course of HRV before ischemic events was compared with the time course of HRV during heart rate-matched nonischemic control periods, using repeated measures. Analysis of variance with two within subjects factors (ischemic event vs. nonischemic control period and repeated HRV assessments: −20 min, −10 min, "event") and post-hoc paired *t* tests. A p level of <0.05 was used as a cut-off for statistical significance.

RESULTS

HRV before ischemic events. A total of 68 ischemic events were recorded (3.6 ± 2.7 episodes per patient, range from 1 to 9) with a mean duration of 9.5 ± 13.3 min (range 2 to 56 min). All ischemic events were asymptomatic. Nonischemic control periods based on matched heart rates were obtained in 13 of the 19 patients (37 episodes).

As shown in Figure 1, a significant decrease in high- and low-frequency HRV was observed in the period preceding the ischemic event (p's < 0.001). High frequency HRV decreased in the 60- to 10-min interval before the ischemic event (p = 0.04). A further decrease was observed between the 4-min and 2-min intervals before the ischemic event (p = 0.008) and from 2 min up to the ischemic event (p = 0.001). Analysis of low frequency HRV demonstrated a similar pattern, but, in contrast with high frequency HRV, no significant change in low frequency HRV was found for the 60-min to 10-min preischemic period (p = 0.71). The low frequency/high frequency ratios did not significantly change over time (p = 0.48).

Postischemic recovery pattern of HRV. After the ST-segments returned to baseline, high frequency HRV remained significantly depressed at 2 min (p = 0.001), 10 min (p = 0.003) and 20 min (p = 0.05) compared with the 60-min preischemic event value (Fig. 1). Results for low-frequency HRV recovery were similar. By 60 min after the ischemic event, both the high and low frequency HRV returned to the baseline value at 60 min before the ischemic event. Further analyses revealed that the sustained postischemic HRV levels were depressed only in events triggered by high levels of mental or physical activities. No significant changes were observed in the low frequency/high frequency ratio during postischemic intervals.

Effects of mental and physical activity. Mental activity assessments were available for 53 of 68 ischemic episodes. Of these, 27 (51%) occurred during high mental activity (score ≥5). The mean duration from activity onset to the ischemic event was 5 ± 3 min. Ischemic events occurring during high levels of mental activity were associated with reduced high frequency HRV (Fig. 2). The difference emerged 10 min before the ischemic event (p = 0.060) and persisted until 4 min (p = 0.038) and 2 min before ischemia (p = 0.045) (main effect p = 0.083). However, the interaction term (high-frequency HRV change × activity level) was not significant ($p_{interaction} > 0.10$), and Holm-corrected p values were nonsignificant (p's > 0.05). As is shown in Figure 2, no effects of mental stress on HRV were noted during the nonischemic heart rate-matched control periods. Thus, reduced high-frequency HRV levels during mental stress occurred specifically before ischemic events and were not an epiphenomenon of increased heart rate.

Mental activities resulted in reduced low frequency HRV levels at 2 min before ischemic events (5.6 ± 1.0 ln [ms^2] vs. 4.8 ± 1.7 ln [ms^2]; p = 0.032), which tended to persist at the onset of ischemia (4.7 ± 1.2 ln [ms^2] vs. 4.1 ± 1.5 ln [ms^2]; p = 0.077). These values became nonsignificant after Holm's correction for familywise error. During the nonischemic control periods, no significant associations were found between mental activity levels and low frequency HRV.

Assessments of physical activity levels were available for 64 of the 68 ischemic events. Thirty-two ischemic events (50%) occurred with high levels of physical activity and 14/32 coincided with simultaneous high mental activities. Low frequency HRV was significantly elevated during high (5.8 ± 1.3 ln [ms^2]) compared with low (5.2 ± 1.4 ln [ms^2]; p = 0.05) levels of physical activity at 10 min before ischemia, whereas high frequency HRV was unrelated to physical activity levels. During nonischemic control periods,

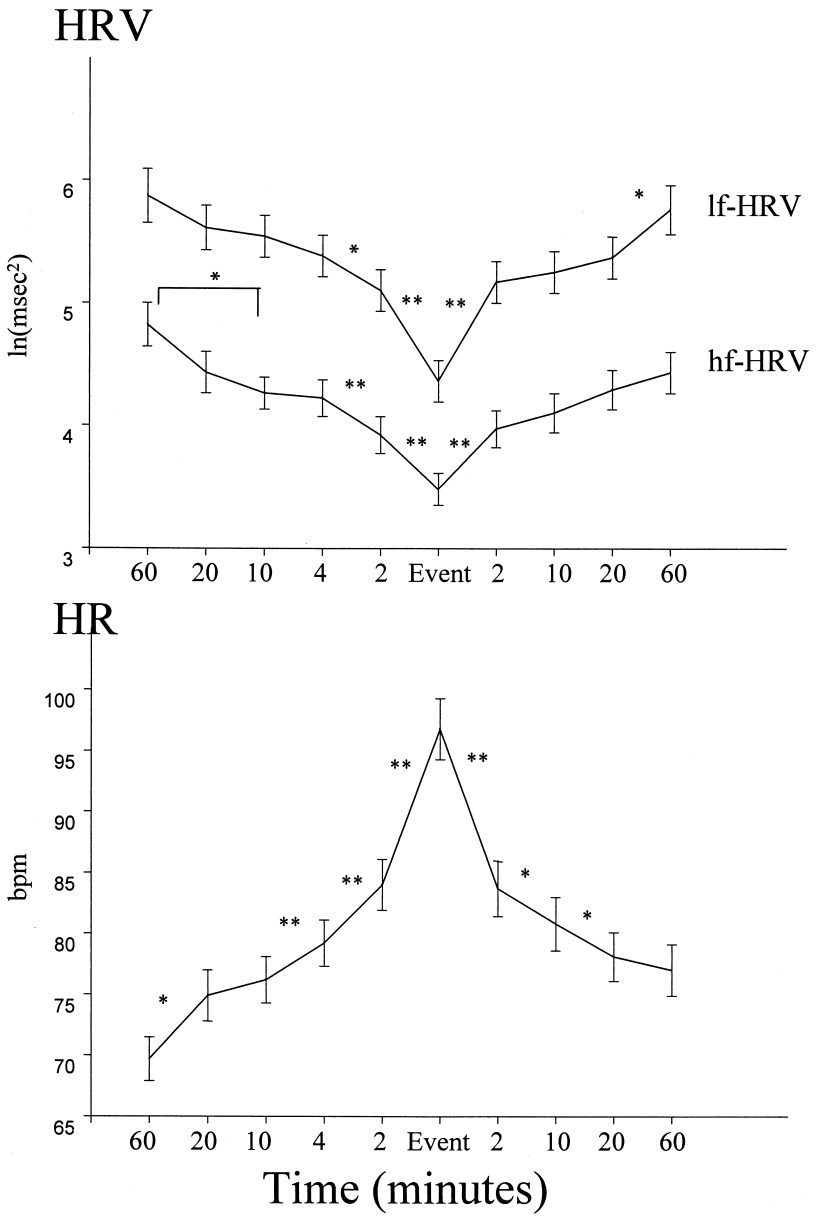

Figure 1. Decrease in heart rate variability (HRV) before ischemic events. **Top:** A significant decrease in high frequency (hf) ($p = 0.04$) occurred in the period from 60 min to 10 min before the ischemic event, followed by a further depression during the 4 min preceding the event. Low frequency (lf) HRV decreased significantly at 4 min before the ischemic event but not at earlier time points. **Lower:** Changes in heart rate (HR) in the hour surrounding ischemic events. *$p < 0.05$; **$p < 0.01$, unadjusted p levels comparing target and preceding HRV or HR level.

no associations were observed between physical activity and either high frequency or low frequency HRV.

Relation between heart rate and HRV. Ischemic events occurring at high heart rates (>100 beats/min; 35 episodes) were associated with lower high frequency HRV (3.1 ± 1.2 ln [ms^2]) than ischemic events at lower heart rates (≤100 beats/min; 3.9 ± 0.8 ln [ms^2]; $p = 0.003$). Low frequency HRV was also depressed during high HR events (3.8 ± 1.5 ln [ms^2] vs. 5.0 ± 1.1 ln [ms^2]; $p = 0.001$), and these differences remained significant after adjustment for multiple comparisons (p's < 0.01). As shown in Figure 3, differences between high versus low heart rate events were only observed at the onset of ischemic events and not during preceding time points (high frequency $p_{interaction} = 0.043$; low frequency $p_{interaction} < 0.001$). The changes in HRV during high HR events coincided with steeper HR increases at the onset of ischemia.

Heart rates gradually increased in the 60-min to 20-min interval before the ischemic event ($p = 0.04$) followed by a more pronounced increase in the 4 min before ischemia ($p = 0.008$). A parallel time course was observed between the HRV decreases and heart rate increases preceding the ischemic event; the magnitude of heart rate increase during the 10 min before the ischemic event was correlated with

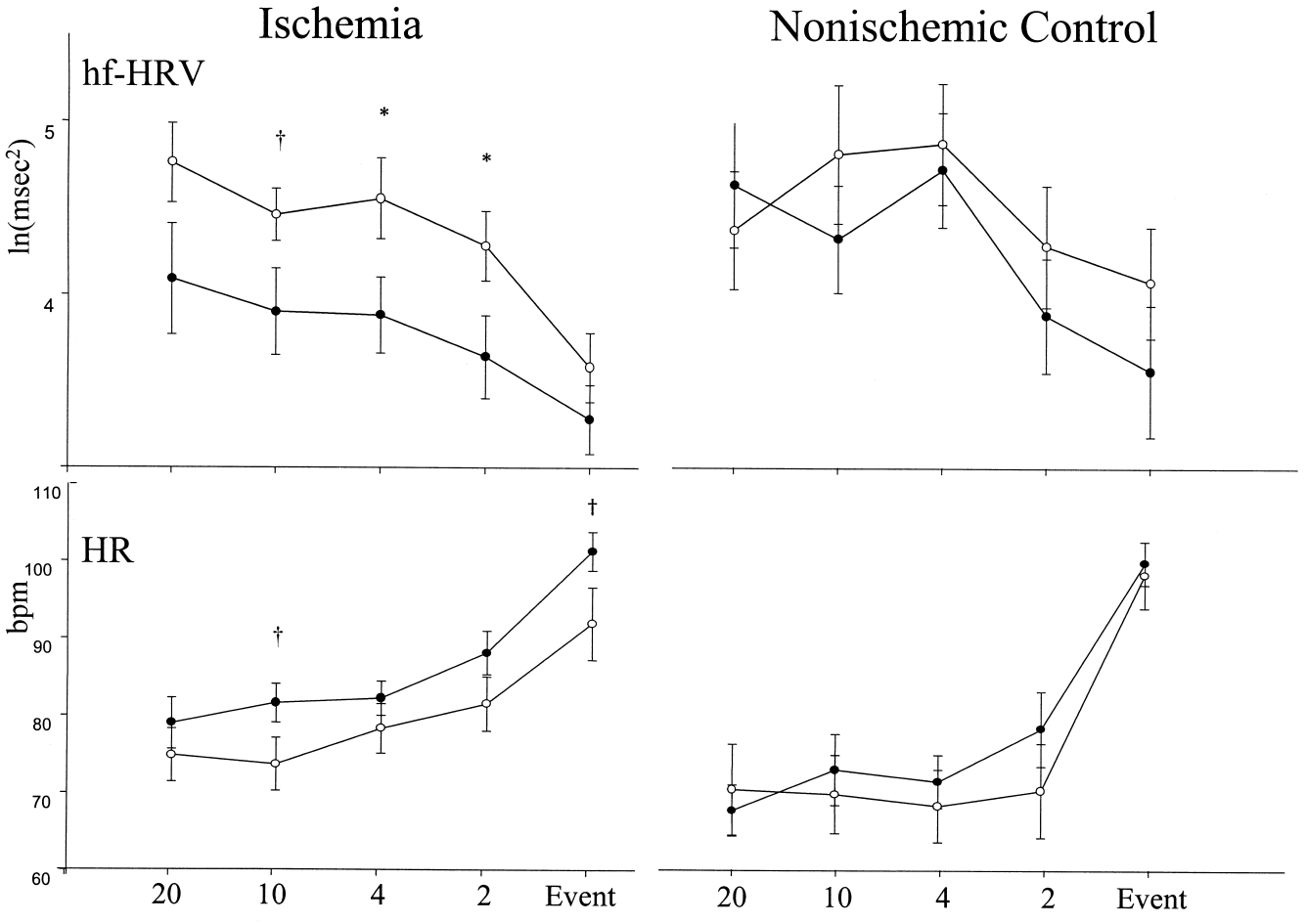

Figure 2. Depressed high-frequency heart rate variability (HRV) during elevated mental activities before ischemic events. High frequency (hf) HRV was significantly depressed during high levels of mental activity compared with events occurring at low mental activity. The difference emerged 10 min before the ischemic event ($p = 0.060$) and persisted until 4 min ($p = 0.038$) and 2 min before ischemia ($p = 0.045$). Heart rates (HR) tended to be elevated during high mental stress at onset of ischemia and 10 min before ischemia. *$p < 0.05$; †$p < 0.10$ (unadjusted p values for high versus low mental activity comparisons). **Solid circle** = high mental activity; **open circle** = low mental activity.

the magnitude of reduction in high frequency HRV ($r = -0.31$, $p = 0.01$) and low frequency HRV ($r = -0.33$, $p = 0.006$).

Table 1 shows heart rate and HRV preceding ischemic events and matched nonischemic control periods (37 episodes; 13 patients). Consistent with the selection criteria, comparable heart rates were found for the ischemic events and nonischemic control periods. No differences were found in HRV components before ischemic events versus heart rate-matched nonischemic control periods, with the exception of lower low frequency HRV at onset of ischemia compared with the heart rate-matched control period ($p = 0.03$, Table 1). The heart rates directly preceding ischemia (at −4 and −2 min) were higher (80.2 ± 17.2 beats/min and 86.0 ± 18.5 beats/min) than heart rates of the corresponding nonischemic control periods (70.8 ± 14.6 beats/min and 73.8 ± 18.5 beats/min, respectively, p's < 0.05), but no significant high frequency HRV differences were observed between ischemic and control periods at those two time points (p's > 0.10). Thus, the overall preischemic changes in HRV occurred to the same extent before nonischemic heart rate-matched periods. However, as shown in Figure 2, high frequency HRV levels were reduced before ischemic events occurring at high mental activity, whereas no such effects of mental stress were noted before heart rate-matched control episodes.

DISCUSSION

This study demonstrates that decreases in HRV precede myocardial ischemia during the activities of daily life. These decreases occur as early as 10 min before the event and are most pronounced in the 4 min before ischemic ST-segment depression. Furthermore, ischemic events occurring at high mental activities were preceded by significantly decreased high frequency HRV levels. These findings suggest that vagal withdrawal precedes the onset of transient myocardial ischemia and may help explain the phenomenon of mental stress-induced ischemia, which typically occurs at low heart rates.

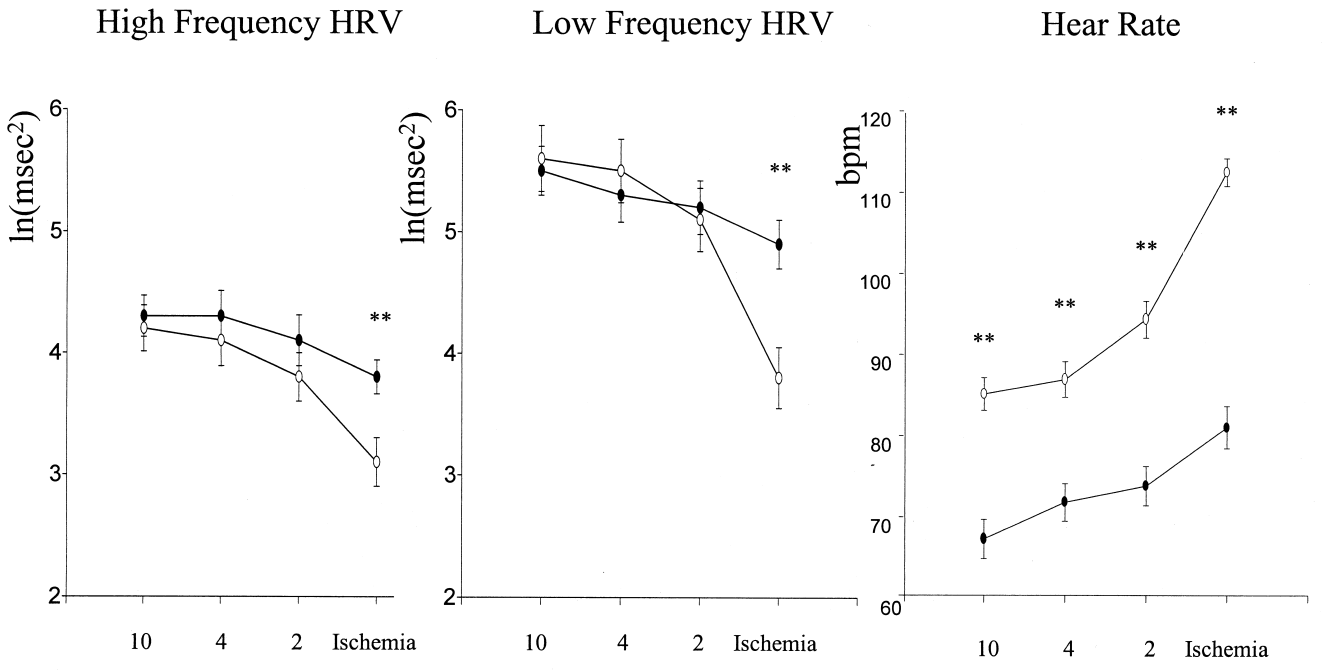

Figure 3. Relation between ischemic heart rate (HR) and heart rate variability (HRV) changes. Both low ($p = 0.001$) and high frequency ($p = 0.003$) HRV components were significantly depressed at ischemic events occurring at high HRs (>100 beats/min; 35 episodes) compared with events occurring at low heart rates (33 episodes. Heart rate variability measures did not differ between high versus low heart rate events for assessments before the ischemic events (at 10, 4 and 2 min; $p_{interaction} < 0.01$). **$p < 0.005$ ischemic events occurring at high versus ischemic events at low HRs. **Open circle** = high HR event; **solid circle** = low HR event.

Ambulatory ischemia and the time course of autonomic changes. The observed preischemic autonomic changes confirm a previous report by Goseki et al. (30). Although the majority of patients in that study (12 of the 19) were monitored without discontinuation of beta-blocking agents, which are known to affect HRV parameters, the results nonetheless indicated significant decreases in high frequency HRV before ischemia. This study demonstrates a similar pattern of vagal withdrawal in patients tested off anti-ischemic medications. Furthermore, the present findings more precisely define the trajectory of postischemic HRV changes, assess the interrelationship between heart rate and HRV changes and evaluate the role of physical and mental activities in HRV changes before ambulatory ischemic events.

Measures of vagal withdrawal were found to persist until 20 min after ischemia. Sustained HRV depression was only observed for events occurring at high activity levels, probably indicating continued engagement or residual effects of these activities. It is also possible that transient ischemia has sustained residual effects on cardiac vagal tone, independent of activity levels, or that ambulatory ischemia persisted for longer than detectable by ST-segment depression. Laboratory studies using sensitive techniques to detect myocardial ischemia such as radionuclide ventriculography or echocardiography are needed to further understand the recovery pattern of HRV after ischemic events.

Association of mental stress with autonomic changes and myocardial ischemia. Several studies indicate a direct association between mental activity and vagal withdrawal (15). This study shows that the vagal withdrawal associated with mental activities appears to be specific to ischemic events because high mental activity levels were associated with HRV decreases in ischemia, but not in nonischemic, control periods. Furthermore, these findings were not confounded by potential influences of perceived pain on autonomic nervous system activation because all ischemic events were asymptomatic. Thus, mental stress may trigger ambulatory

Table 1. Time Trajectory of High and Low Frequency HRV Components Before Ischemia and Heart Rate-matched Nonischemic Control Periods (Mean ± SD)

Time Before Ischemic Event	Heart Rate (beats/min)		High Frequency HRV ln (ms^2)		Low Frequency HRV ln (ms^2)	
	Ischemia	Control	Ischemia	Control	Ischemia	Control
20 min	75.0 ± 16.2	71.5 ± 14.5	4.58 ± 1.23	4.89 ± 1.40	5.77 ± 1.27	6.14 ± 1.42
10 min	76.7 ± 17.0	73.6 ± 14.6	4.39 ± 1.19	4.64 ± 1.54	5.70 ± 1.30	5.92 ± 1.61
Ischemia	98.9 ± 20.5	98.5 ± 19.1	3.75 ± 1.06	4.01 ± 1.35	4.79 ± 1.30	5.43 ± 1.61*

*$p < 0.05$, ischemic event vs. nonischemic control.
HRV = heart rate variability.

ischemia only if sufficient vagal withdrawal is elicited by the activity.

Relations between heart rate and HRV before ambulatory ischemia. Heart rate and HRV are not independent factors (5), and, for that reason, analyses were performed examining heart rate-matched control periods. From a practical perspective, there would be no need for complex HRV analyses in future studies on triggers of ambulatory ischemia if the same information could be obtained by the simple assessments of heart rate alone. Mental stress-induced ischemia in the laboratory and ambulatory ischemia typically occur at lower heart rates than observed during clinical exercise testing with rapidly increasing work loads (11,31). This study demonstrates similar heart rates for ambulatory ischemic events triggered by mental stress as compared with events triggered by exercise. The main difference between exercise and mental stress-induced ischemia may, therefore, be that a decrease in high-frequency HRV characterizes mental stress-induced ischemia. Patterns of HRV preceding ischemic events did not significantly differ from HRV changes during nonischemic heart rate-matched control periods. This may suggest that vagal withdrawal, as observed before ischemia, also occurs at episodes of increased heart rate in the absence of electrocardiographic apparent ischemia. There are several reasons that may account for the lack of differences in HRV before ischemic events versus nonischemic control periods. First, the ECG is not sensitive to detecting ischemia at low heart rates and may, therefore, incorrectly indicate the absence of ischemia in "nonischemic" control periods. Second, it may not be feasible to completely separate HRV and heart rate because withdrawal of cardiac vagal tone causes an increase in heart rate (5). On the other hand, we documented that high mental activity was associated with a decrease in HRV variability before ischemic events but not in heart rate-matched nonischemic control periods, which supports the independent nature of heart rate and HRV changes in mental stress-induced ischemia. Furthermore, it is also important to note that the high frequency component of HRV is a substantially more accurate indicator of vagal tone compared with heart rate per se (5,18,27), and prospective studies have demonstrated differential predictive value of HRV over heart rate for adverse long-term prognosis of cardiovascular disease (18,27).

Study limitations. Results of this study may not be applicable to all coronary disease patients because only male patients with stable disease were examined. In addition, because this study examined precipitants of ambulatory ischemia, we were limited to the use of electrocardiographic assessments of autonomic changes and myocardial ischemia and not able to control for confounding effects of breathing frequency.

Because this study uses ambulatory techniques to assess autonomic and behavioral precipitants of ambulatory ischemia, the occurrence of study variables were based on observation and were not under experimental control. We also evaluated HRV changes preceding ischemic "events" as a unit of analyses, rather than the "patient." More commonalities in precipitating factors of ambulatory ischemia are observed within multiple events of one individual patient than in the same number of events but in different patients. To further disentangle the role of daily life activities and preischemic autonomic changes in ambulatory settings, future studies are required using a time-dependent analysis of covariance and time-series analysis in larger groups of patients.

Heart rate variability is an indirect measure of cardiac autonomic tone; direct measures of neural activity are not feasible during ambulatory studies. The relatively low sampling rate (128 Hz) is not optimal for the assessment of low frequency HRV. Although this objection does not affect the high frequency HRV results, the low frequency findings may have been attenuated. Further developments of digital ambulatory ECG registration devices may provide opportunities to increase precision in the measurement of these HRV parameters.

Clinical implications. This study indicates that activity-induced changes in the sympathovagal balance are involved in triggering myocardial ischemia. The prognostic value of decreased HRV for cardiac disease progression may, therefore, be mediated, in part, by exercise and mental stress-induced autonomic changes. Beta-blockers have been shown to enhance vagal activity measured on the HRV time and frequency domains (32). Thus, beta-blockade may be beneficial in the treatment of myocardial ischemia by simultaneously reducing cardiac demand and increasing vagal tone. Since this study demonstrates that decreased vagal activity occurs as early as 10 min before the electrocardiographic evidence of ischemia, it is conceivable that a vagomimetic agent such as scopolamine will be beneficial for the treatment of refractory myocardial ischemia. Further research is needed to investigate this possibility.

Reprint requests and correspondence: Dr. Willem J. Kop, Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20814. E-mail wjkop@mxb.usuhs.mil.

REFERENCES

1. Pozzati A, Pancaldi LG, Di Pasquale G, Pinelli G, Bugiardini R. Transient sympathovagal imbalance triggers "ischemic" sudden death in patients undergoing electrocardiographic Holter monitoring. J Am Coll Cardiol 1996;27:847–52.
2. Martin GJ, Magid NM, Myers G, et al. Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. Am J Cardiol 1987;60:86–9.
3. Kienzle MG, Ferguson DW, Birkett CL, Myers GA, Berg WJ, Mariano DJ. Clinical, hemodynamic and sympathetic neural correlates of heart rate variability in congestive heart failure. Am J Cardiol 1992;69:761–7.
4. Stein KM, Borer JS, Okin PM, Kligfield P. Prognostic value of heart rate variability measures in patients with chronic, nonischemic mitral regurgitation. J Electrocardiol 1992;25 Suppl:220.
5. Bigger JT, Jr, Hoover CA, Steinman RC, Rolnitzky LM, Fleiss JL. Autonomic nervous system activity during myocardial ischemia in man

estimated by power spectral analysis of heart period variability: the Multicenter Study of Silent Myocardial Ischemia investigators. Am J Cardiol 1990;66:497–8.
6. Breuer HW, Skyschally A, Schulz R, Martin C, Wehr M, Heusch G. Heart rate variability and circulating catecholamine concentrations during steady-state exercise in healthy volunteers. Br Heart J 1993;70: 144–9.
7. Yamamoto Y, Hughson RL, Peterson JC. Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. J Appl Physiol 1991;71:1136–42.
8. Tulppo MP, Makikallio TH, Takala TE, Seppanen T, Huikuri HV. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. Am J Physiol 1996;271:H244–52.
9. Kovach JA, Gottdiener JS, Verrier RL. Vagal modulation of epicardial coronary artery size in dogs: a two-dimensional intravascular ultrasound study. Circulation 1995;92:2291–8.
10. Goldberg AD, Becker LC, Bonsall R, et al. Ischemic, hemodynamic and neurohormonal responses to mental and exercise stress: experience from the Psychophysiological Investigations of Myocardial Ischemia study (PIMI). Circulation 1996;94:2402–9.
11. Rozanski A, Bairey CN, Krantz DS, et al. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. N Engl J Med 1988;318:1005–12.
12. Burg MM, Jain D, Soufer R, Kerns RD, Zaret BL. Role of behavioral and psychological factors in mental stress-induced silent left ventricular dysfunction in coronary artery disease. J Am Coll Cardiol 1993;22:440–8.
13. Blumenthal JA, Jiang W, Waugh RA, et al. Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life: association and hemodynamic features. Circulation 1995;92:2102–8.
14. Pagani M, Furlan R, Pizzinelli P, Crivellaro W, Cerutti S, Malliani A. Spectral analysis of R-R and arterial pressure variabilities to assess sympathovagal interaction during mental stress in humans. J Hypertens Suppl 1989;7:S14–5.
15. Tuininga YS, Crijns HJ, Brouwer J, et al. Evaluation of importance of central effects of atenolol and metoprolol measured by heart rate variability during mental performance tasks, physical exercise, and daily life in stable postinfarct patients. Circulation 1995;92:3415–23.
16. McCraty R, Atkinson M, Tiller WA, Rein G, Watkins AD. The effects of emotions on short-term power spectrum analysis of heart rate variability. Am J Cardiol 1995;76:1089–93.
17. Pagani M, Mazzuero G, Ferrari A, et al. Sympathovagal interaction during mental stress: a study using spectral analysis of heart rate variability in healthy control subjects and patients with a prior myocardial infarction. Circulation 1991;83:II43–51.
18. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043–65.
19. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220–2.
20. Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985;248:H151–3.
21. Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation 1997;96:3224–32.
22. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation 1993;88:927–34.
23. Freed LA, Stein KM, Gordon M, Urban M, Kligfield P. Reproducibility of power spectral measures of heart rate variability obtained from short-term sampling periods. Am J Cardiol 1994;74:972–3.
24. Krantz DS, Kop WJ, Gabbay F, et al. Circadian variation of ambulatory ischemia: triggering by daily activities and evidence for an endogenous circadian component. Circulation 1996;93:1364–71.
25. Gabbay FH, Krantz DS, Kop WJ, et al. Triggers of myocardial ischemia during daily life in patients with coronary artery disease: physical and mental activities, anger and smoking. J Am Coll Cardiol 1996;27:585–92.
26. Pardo Y, Merz CN, Paul-Labrador M, et al. Heart rate variability reproducibility and stability using commercially available equipment in coronary artery disease with daily life myocardial ischemia. Am J Cardiol 1996;78:866–70.
27. Berntson GG, Bigger JT, Eckberg DL, et al. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 1997;34: 623–48.
28. Patterson S, Krantz D, Montgomery L, Deuster P, Hedges S, Nebel L. Automated physical activity monitoring: validation and comparison with physiological and self-report measures. Psychophysiology 1994; 30:296–305.
29. Gottdiener JS, Krantz DS, Howell RH, et al. Induction of silent myocardial ischemia with mental stress testing: relation to the triggers of ischemia during daily life activities and to ischemic functional severity. J Am Coll Cardiol 1994;24:1645–51.
30. Goseki Y, Matsubara T, Takahashi N, Takeuchi T, Ibukiyama C. Heart rate variability before the occurrence of silent myocardial ischemia during ambulatory monitoring. Am J Cardiol 1994;73:845–9.
31. Krantz DS, Kop WJ, Santiago HT, Gottdiener JS. Mental stress as a trigger of myocardial ischemia and infarction. Cardiol Clin 1996;14: 271–87.
32. Keeley EC, Page RL, Lange RA, Willard JE, Landau C, Hillis LD. Influence of metoprolol on heart rate variability in survivors of remote myocardial infarction. Am J Cardiol 1996;77:557–60.