Mental Stress–Induced Ischemia in the Laboratory and Ambulatory Ischemia During Daily Life
Association and Hemodynamic Features

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**Background** The purpose of this study was to determine the correspondence of mental stress–induced ischemia in the laboratory with ambulatory ischemia and to assess the relationship between hemodynamic responses to mental stress and the occurrence of ischemia. Although exercise testing is usually used to elicit myocardial ischemia, ischemia during daily life usually occurs at relatively low heart rates and in the absence of strenuous physical exercise. Mental stress has been shown to trigger ischemic events in the laboratory at lower heart rates but at blood pressures comparable to exercise. We therefore compared the extent to which mental stress and exercise testing identify patients who develop ischemia out of hospital.

**Methods and Results** One hundred thirty-two patients with documented coronary disease and recent evidence of exercise-induced myocardial ischemia underwent 24-hour ambulatory monitoring and radionuclide ventriculography during exercise and mental stress testing. Patients who displayed mental stress–induced ischemia in the laboratory were more likely to exhibit ischemia during daily life ($P<.021$). Furthermore, patients exhibited ischemia during ambulatory monitoring of larger diastolic blood pressures ($P<.006$), heart rate ($P$) and rate-pressure product responses ($P<.018$) during stress.

**Conclusions** Among patients with prior positive stress tests, mental stress–induced ischemia, defined as wall motion abnormalities, predicts daily ischemia independent of exercise-induced ischemia. Exaggerated hemodynamic responses during mental stress testing also identify those who are more likely to exhibit myocardial ischemia during daily life and mental stress. *(Circulation, 1995;92:2102-2108)*

**Keywords** ischemia • stress • hemodynamic relationship between laboratory-induced myocardial ischemia and ambulatory ischemia in patients with coronary artery disease. Although mental stress ischemia occurs at lower heart rates than exercise ischemia, arterial pressure elevations can be substantial. Thus, dynamic determinants of myocardial demand may be a role in low heart rate–related ischemia with stress.

The present study assessed the relationship of ischemia in response to mental stress and exercise to the laboratory, defined either by RNN or ECG ischemia measured by ambulatory ECG monitoring. Because the mechanisms of mental stress and ischemia may be different, we also compared the hemodynamic responses in the laboratory exercise and mental stress and assessed whether dynamic responses elicited in the laboratory were predictive of ischemia in the laboratory or during daily life.

**Methods**

One hundred thirty-two patients (117 men, 15 women) aged 36 to 74 years (mean age, 58.5 ± 8.4 years) with documented coronary disease (by prior myocardial infarction, artery bypass graft surgery, coronary angioplasty, and stenting in at least one of the major coronary arteries) and ischemia in the laboratory (remote to recent (<1 year) evidence of exercise-induced ischemia) were studied. Sixty-four (48%) subjects had a prior MI, 41 (31%) had CAGB, and 41 (31%) had a history of PTCA. Pati
Selected Abbreviations and Acronyms

CABG = coronary artery bypass grafting
LVEF = left ventricular ejection fraction
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
RNV = radionuclide ventriculography
TMJ = transient myocardial ischemia
WMA = wall motion abnormality (abnormalities)

urc. severe cardiac arrhythmias, left bundle-branch block, Wolf-Parkinson-White syndrome, resting blood pressure >200/120 mm Hg, left ventricular ejection fraction <30%, or left main coronary artery stenosis ≥50% were excluded. This study was approved by the Institutional Review Board at Duke University Medical Center, and informed consent was obtained from all subjects before their participation.

Ambulatory ECG Monitoring

Patients were withdrawn from β-blockers, calcium channel blockers, and long-acting nitrates at least 48 hours before testing; one patient with exercise-induced ischemia on medications was not withdrawn. All patients were instrumented between 9 and 11 AM. An AAMI tape-based, three-channel Holter ECG recorder (Zymed Inc) was used for ambulatory ischemic monitoring after careful skin preparation, postural testing, and calibration. Modified V1, V4, and aVF leads were selected for detecting ST segment variation.

ST segment analysis was performed on the Marquette series 8000 laser Holter system (Marquette Electronic Inc). Tapes were read at 500 times real time, and ECG data were digitized. Episodes of ST segment depression were examined by a cardiologist after all QRS complexes were classified. Myocardial ischemia was defined as horizontal or downslowing ST segment depression of ≥1 mm (0.1 mV) for ≥1 minute compared with baseline. The termination of an ischemic episode was determined at the time the ST segment depression returned to ≤0.9 mm (0.09 mV) of the baseline for ≥1 minute. If the ST segments became redepresed within 1 minute for ≥1 additional minute, the episodes were bridged as one. Ischemic burden was quantified as the area under the curve, i.e., the magnitude of ST segment depression from the isoelectric line multiplied by duration of the ischemic episode. ST segment depression associated with ventricular tachycardia or frequent ventricular beats were excluded from analysis. Consensus was obtained for each ECG reading from two cardiologists who were blinded to the patient’s identity and clinical data.

Mental and Exercise Stress Testing

On a separate day, while patients were still off anti-ischemic medications, they underwent a series of laboratory challenges and exercise stress testing using bicycle ergometry.

Mental Stress Testing

After a 40-minute calibration-rest period, subjects were asked to complete a series of mental stress tasks. (1) Mental arithmetic—Patients were asked to perform a series of serial additions, with encouragement to perform calculations as quickly as possible. (2) Public speaking—Patients were asked to give a speech on a current event topic to an audience of observers after 1 minute of preparation. Subjects were told that their speech would be evaluated. (3) Mirror trace—Subjects were asked to outline a star from its reflection in a mirror as quickly as possible. (4) Reading—Subjects read an easy-to-read and neutral passage selected from Reader’s Digest or North Carolina Wildlife magazine. (5) Type A structured interview—Patients underwent a standard videotaped interview to assess type A behavior.15 The type A interview typically lasts 20 minutes, although the RNV acquisition was obtained for only 2 minutes after the question dealing with anger, which usually occurred after 1 to 2 minutes after the start of the interview (e.g., “When you get angry or upset, do people around you know about it?”). Exercise was given last for all patients. Each task lasted 3 minutes (except for the type A interview), with a 6-minute rest period between each stressor.

Exercise Testing

After the series of mental stressors and after a 20-minute rest period, patients exercised on a cycle ergometer in the upright position at a beginning level of 25 W. Exercise workload was increased by 25 W every 2 minutes. Exercise was terminated when the following occurred: (1) 90% of the patient’s predicted maximal heart rate was reached; (2) moderate to severe chest pain; (3) ST segment depression of ≥2 mm from baseline; (4) blood pressure decreased by ≥20 mm Hg; (5) malignant ventricular arrhythmia; or (6) dyspnea or severe fatigue.

Physiological Measures

Hemodynamic Measures

A standard 12-lead ECG was recorded with a Quinton Electrocardiograph (Quinton Electronics) at 1-minute intervals during the rest period, mental stress testing, and exercise testing. Heart rate was determined from the ECG. Blood pressure was measured every minute with an automatic oscillographic blood pressure monitor (Quinton Electronics). Hemodynamic responses—systolic and diastolic blood pressures, heart rate, and rate-pressure product—were obtained by subtracting the initial baseline level from the mean level recorded during each task.

Radionuclide Ventriculography

A wave-synchronized, multiple-gated equilibrium RNV with PARAGON EPR (Medaxis Inc) was performed at 20 frames per second with the use of a mobile gamma camera (Siemens Germany-Sonics Inc) equipped with a 0.25-in sodium iodide crystal and an all-purpose collimator. Images were obtained after the labeling of autologous red blood cells with 99mTc pertechnetate by the in vivo technique.14 Imaging acquisitions were obtained during the last 2 minutes of the rest period, the first 2 minutes of each stressor (except for the interview, which was keyed to a question dealing with anger), and at peak exercise with the camera positioned in the best septal–left anterior oblique view. LVEF was obtained using the software of the EPR system. Segmental wall motion of the left ventricle (high and low posterolateral, inferoapical, and septal walls) was later assessed visually through the observation of a continuous-loop video display of the images after filtering algorithms were applied. Wall motion was rated by a consensus of experienced physicians, all of whom were blinded to image-related activities (that is, which task was being viewed). Segmental wall motion ratings were assigned the following values: 1: normal; 2: mild hypokinesia; 3: severe hypokinesia; 4: mild akinesia; 5: severe akinesia; 6: mild dyskinesia; and 7: severe dyskinesia. A mild wall motion abnormality involved ≤50% of the wall being evaluated, whereas a severe wall motion abnor-

Table 1. Number of Subjects Exhibiting Ischemia by Mental Stress Task

<table>
<thead>
<tr>
<th>Task</th>
<th>Wall Motion Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Math</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Speech</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Trace</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Read</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Interview</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate number of subjects who experienced ischemia during that task.
mality involved >50% of the wall. Laboratory-induced myocardial ischemia was defined as a change of ≥1 (on the 1 to 7 scale) from baseline for any of the four wall segments. Previous studies have found this technique to be reliable and valid. To determine the reliability of our consensus ratings, we performed two independent consensus ratings on a random sample of 42 subjects. The intraclass correlation used for repeated-measures reliability estimates was .93, confirming the reliability of our RNK consensus ratings.

Data Analysis

We compared the relationship of ambulatory and Holter ischemia using χ² analyses. To assess patterns of hemodynamic responses, we performed a repeated-measures ANCOVA, with task as a within-subjects factor and ischemia group (presence or absence of ischemia by Holter or laboratory mental stress) as the between-subjects factor. Separate analyses were performed for the ischemia group defined by ambulatory and laboratory ischemia. Age, baseline (resting) hemodynamic levels, and resting LVEF were used as covariates in all analyses. A two-tailed probability level of .05 was adopted as significant for all analyses.

Results

Laboratory Ischemia During Mental Stress and Exercise

New WMA were observed in 45 of 132 patients (34%) during mental stress testing and in 65 patients (49%) during exercise. Of the 45 patients who had WMA during mental stress, 33 (73%) exhibited WMA with exercise. Of the 65 patients who had WMA during exercise, 33 (51%) exhibited WMA during mental stress. No patients had ECG evidence of ischemia during mental stress; 44 had ECG evidence of ischemia during exercise.

Table 1 shows the frequency of mental stress-WMA associated with each task. The mirror task elicited the most ischemic events: the speech task, and type A interview together identified (100%) of patients with mental stress–induced ischemia.

### Table 2. Demographic and Clinical Characteristics of Sample

<table>
<thead>
<tr>
<th></th>
<th>Ambulatory TMI</th>
<th>Mental Stress TMI</th>
<th>Entire Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mean age, y (±SD)</td>
<td>59.4 (±8.5)</td>
<td>57.8 (±6.4)</td>
<td>60.7 (±7.3)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>51 (39)</td>
<td>66 (50)</td>
<td>39 (30)</td>
</tr>
<tr>
<td>Smoking history, No. (%)</td>
<td>44 (33)</td>
<td>56 (42)</td>
<td>36 (29)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>12 (9)</td>
<td>7 (6)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>22 (17)</td>
<td>28 (21)</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Prior MI, No. (%)</td>
<td>25 (19)</td>
<td>39 (30)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Prior CABG, No. (%)</td>
<td>21 (16)</td>
<td>24 (18)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Prior PTCA, No. (%)</td>
<td>12 (9)</td>
<td>29 (22)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Hyperlipidemic, No. (%)</td>
<td>38 (29)</td>
<td>49 (37)</td>
<td>29 (22)</td>
</tr>
<tr>
<td>β-Blocker, No. (%)</td>
<td>32 (24)</td>
<td>37 (28)</td>
<td>24 (18)</td>
</tr>
</tbody>
</table>

Ambulatory Ischemia

Fifty-eight patients (44%) exhibited ECG myocardial ischemia during 48 hours of ambulatory monitoring. Table 1 displays the number of Holter ischemic events observed for the entire sample. Patients with Holter ischemia had a mean 7.1 ischemic episodes (SD=9.67); the mode and median were 1 episodes, respectively.

Clinical Characteristics of Patients With Ambulatory Ischemia

Patients with and without TMI assessed during the exercise testing did not differ significantly with respect to cardiac history, medication, angiographic evas, or coronary artery disease, or resting left ventricular ejection fraction (Table 2). There were no differences in the graphic or clinical characteristics of patients with and without stress–induced TMI (Table 2).

Relationship Between Laboratory and Ambulatory Ischemia

A comparison of mental stress–induced ischemia revealed that patients with TMI were more likely to exhibit ischemia during exercise (χ²(1)=5.31, P<.021 [Fig 2]).

Of the 58 patients who exhibited ambulatory ischemia, 26 (45%) displayed WMA during mental stress only 19 (26%) of the 74 patients who did not exhibit ambulatory ischemia displayed WMA. Interestingly, ischemia–induced ischemia, defined by the presence or worsening WMA, was unrelated to ambulatory ischemia (P>.157). Patients who had ECG evidence of ischemia–induced ischemia, however, were more likely to display ambulatory ischemia (P<.02). Although association of ambulatory to exercise ischemia as assessed by ECG was similar in magnitude, they were not redundant. A regression model was estimated in which exercise ischemia and mental stress WMA were ent
hierarchical fashion as predictors of ambulatory ischemia. The addition of mental stress wall motion scores to the equation with only exercise ECG ischemia yielded a significant increment in the model’s predictive power (−2 log L change, 7.801; 1 df, P < .05), indicating that mental stress ischemia was uniquely associated with ambulatory ischemia over and above exercise ECG ischemia. The relative risk associated with ECG exercise ischemia was 3.65 (P < .001) and for mental stress WMA ischemia was 2.98 (P < .007).

**Relationship Between Hemodynamic Responses and Mental Stress–Induced Ischemia**

Analyses of systolic and diastolic blood pressures, heart rate, and double product revealed different magnitudes of hemodynamic response among the different stressors (P < .0001). The largest hemodynamic responses were produced by the public speaking task. Fig 3 shows that patients who exhibited ischemia during the mental stress testing displayed larger systolic blood pressure (P < .003) and rate-pressure product responses (P < .03) across the series of mental stressors than patients who did not exhibit ischemia. Heart rate responses were not different between the two groups (P < .63). For diastolic blood pressure responses, there was a group by task interaction (P < .028), with ischemic patients displaying larger responses than nonischemic patients during public speaking.

**Relationship Between Hemodynamic Responses and Ambulatory Ischemia**

Fig 4 shows that patients who exhibited ischemia during Holter monitoring displayed larger diastolic blood pressure (P < .006), heart rate (P < .039), rate-pressure product (P < .018), and a trend toward larger systolic blood pressure responses (P < .074) than those who did not exhibit ischemia.

Because the data were not normally distributed and there was a wide range in the number of ischemic events (0 to 45) and the total ischemic burden (0 to 3515 mV/min), we compared ischemic activity among high and low diastolic blood pressure reactors using the Wilcoxon rank sum test. High diastolic blood pressure responders were associated with more ischemic episodes (P < .022) and a greater ischemic burden (P < .0379) compared with low diastolic blood pressure responders.

**Comparison of Hemodynamic Responses During Exercise and Mental Stress**

Responses during exercise and mental stress were compared with the use of the public speaking task, which was associated with the largest hemodynamic responses. Compared with exercise, public speaking was associated with less significant increases in heart rate (M_{diff}=48.7±1.8 beats per minute [bpm]; P < .0001), systolic blood pressure (M_{diff}=23.7±2.6 mm Hg; P < .0001), and rate-pressure product (M_{diff}=12,557±531 mm Hg×bpm; P < .0001) and greater increases in diastolic blood pressure (M_{diff}=4.5±1.3 mm Hg; P < .0006). Comparison of the hemodynamic responses between ischemic and nonischemic patients re-
revealed that ischemic patients had larger responses to the speech stress relative to exercise in diastolic blood pressure \( (P<.035) \), systolic blood pressure \( (P<.0003) \), rate-pressure product \( (P<.006) \), and heart rate \( (P<.044) \).

**Discussion**

This study demonstrates that patients who develop myocardial ischemia in response to mental stress are more likely to display ischemia out of hospital than those who do not. Radionuclide WMA during laboratory mental stress were found to be a better predictor of ambulatory ischemia than radionuclide WMA during exercise testing in this group of patients who had a history of positive exercise testing. Although the presence of new or worsening WMA during exercise testing was not related significantly to ambulatory ECG ischemia, ischemia during exercise testing, defined by ECG changes, was related to ambulatory ischemia. However, WMA induced by mental stress were associated with ambulatory ischemia independent of ECG exercise ischemia.

The RNV technique was better able to identify patients who exhibited ambulatory ECG ischemia than the ECG during mental stress testing (no patients exhibited ECG ischemia during mental stress). It is possible that the laboratory mental stress ischemic episodes were less severe and shorter in duration and were more easily detected by RNV than ECG. Ischemia detected by RNV may represent a more subtle form of ischemia that is not readily detected by ECG. Perhaps only in the more severe episodes triggered by exercise was the ECG able to detect ischemia in the laboratory. Because most ambulatory ischemic events occur at relatively low heart rates and during rest or light physical activities, it is not surprising that exercise is not as strongly related to ambulatory ischemia compared with mental stress. Indeed, mental stress testing may reproduce more closely the fluctuations of myocardial oxygen supply and demand, ischemia, determined by wall motion abnormality by two-dimensional echocardiography, with increased ischemic activities in a sample of 19 card. Although our data confirm their finding of ischemia during sedentary activities, he study lacked adequate power, or subjects differed in their level of physical activity has been shown to inversely related activity. 19

Results of this study also suggest that myocardial ischemia during mental stress and daily life respond with increased heart rate and pressure product to laboratory mental stress. Because hemodynamic responses during monitoring was not performed, we are unable to attribute ambulatory ischemia to exaggerated hemodynamic responses during daily life. However, mental stress-induced ischemia display greater blood pressure and rate-pressure product than larger diastolic blood pressure responses while speaking, and patients who display ambulatory ischemia exhibit higher diastolic blood pressure, heart rate, and rate-pressure product increases during mental stress testing. Although increased hemodynamic responses could be a consequence rather than cause of myocardial ischemia, this possibility is unlikely for several reasons. First, the observed hemodynamic changes coincided with the onset of the mental stress, and ischemia either maintained or declined very gradually during a 2-minute interval during which the ventricular wall motion measurements were acquired. Ischemia-provoking hemodynamic responses might have been expected to occur further rather than be steady or slowly decline because few of the mental stress tests.
These results are consistent with several other studies that have examined the relationship between the propensity toward increased hemodynamic responses and mental stress–induced ischemia in the laboratory. Systolic blood pressure is an important determinant of myocardial oxygen demand in patients with easily inducible myocardial ischemia. However, the occurrence of myocardial ischemia at low heart rates during ambulatory monitoring suggests that factors which decrease myocardial blood flow also may contribute to the development of myocardial ischemia. This possibility is supported by coronary angiographic studies that demonstrate paradoxical coronary vasoconstriction in response to environmental stimuli that can trigger ischemia.

The finding that heightened diastolic blood pressure responses distinguish patients with those without myocardial ischemia both in the laboratory and ambulatory settings also is consistent with the hypothesis that reduced blood supply may be operative. It has been postulated that vasoconstriction (inferred from heightened diastolic blood pressure) may also occur in the coronary arteries or coronary microcirculation, resulting in reduced blood flow to the myocardium. This hypothesis is supported by the recent observation that higher levels of diastolic blood pressure (at comparable ejection fraction falls) occurred during mental stress relative to exercise testing.

We noted that ischemic patients’ hemodynamic responses during public speaking stress were associated with higher diastolic blood pressure responses but lower heart rate and rate-pressure product responses compared with responses during exercise. This pattern suggests a different pathophysiology for mental stress ischemia compared with exercise-induced ischemia and is consistent with a recent report indicating that mental stress–induced left ventricular dysfunction was accompanied by a smaller increase in rate-pressure product compared with exercise.

Clinical Significance

Because mental stress–induced ischemia is more likely to be associated with ambulatory ischemia than exercise-induced ischemia, mental stress testing may help to identify patients at risk for exhibiting transient myocardial ischemia during daily life. Determining the susceptibility of individuals to mental stress–induced ischemia may be helpful in guiding therapeutic efforts to reduce myocardial damage. Attenuation of hemodynamic responses to mental stress by pharmacological or behavioral therapies might be one approach to reduce ischemic activity. Animal studies have shown that surgically lowering heart rate may retard progression of coronary atherosclerosis, and administration of β-adrenergic blockade also slows disease progression, possibly by reducing hemodynamic responses. Exercise training also attenuates cardiovascular and neuroendocrine responses to mental stress in humans without myocardial ischemia. Furthermore, recent studies have shown that exercise may reduce ischemia in cardiac patients during daily life as well as exercise stress testing. Thus, attenuation of hemodynamic responses to mental stress

Acknowledgments

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References


