Prognostic Value of Mental Stress Testing in Coronary Artery Disease*

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This study assesses the prognostic value of mental stress-induced ischemic left ventricular wall motion abnormalities and hemodynamic responses in patients with stable coronary artery disease (CAD). Seventy-nine patients (76 men and 3 women) with prior positive exercise test results were exposed to mental arithmetic and a simulated public speech stress in 2 prior studies. Ischemic wall motion abnormalities were monitored using echocardiography or radionuclide ventriculography (RNV). During mental stress testing, new or worsened ischemic wall motion abnormalities to mental stress and exercise were ascertained, as were peak changes in blood pressure and heart rate to mental stress. The occurrence of subsequent cardiac events (including cardiac death, nonfatal myocardial infarction, or revascularization procedures) was ascertained. New cardiac events were observed in 28 of 79 patients (35%) after a median follow-up duration of 3.5 years (range 2.7 to 7.3). Survival analysis indicated that 20 of 45 patients with mental stress ischemia (44%) experienced new cardiac events more frequently than those without mental stress ischemia (8 of 34; 23%; p = 0.048). Type of cardiac event did not differ between mental stress-positive and stress-negative patients. After controlling for baseline blood pressure and study group status (echocardiography vs RNV), there was a significantly higher relative risk of subsequent events for patients with high versus low peak stress-induced diastolic blood pressure responses (RR = 2.4, confidence interval 1.1 to 5.2; p = 0.03). These results demonstrate that ischemic and hemodynamic measures obtained from mental stress testing may be useful in assessing prognosis in CAD patients with prior positive exercise test results.

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Evidence indicates that mental stress can induce myocardial ischemia in 30% to 60% of patients with coronary artery disease (CAD).[1–4] Mental stress-induced ischemia occurs at lower heart rate thresholds than exercise ischemia, but at blood pressure elevations comparable to exercise ischemia,[3] and is generally observed among patients with exercise ischemia.[1,4] Although the prognostic value of exercise-induced left ventricular dysfunction for cardiac events is well established,[5–7] only 2 recent studies suggest that mental stress-induced ischemia may have prognostic significance. In a small saple of stable patients with CAD, Jain et al[8] reported that, compared to patients with normal responses to mental stress, those with decreases in left ventricular ejection fraction to stress experienced a higher cardiac event rate at 2-year follow-up. In a larger sample of stable patients followed for 3 years, Jiang et al[9] observed that mental stress-induced ejection fraction decreases were associated with elevated risk of new fatal and nonfatal myocardial infarction, coronary bypass, and/or angioplasty. In addition to ischemic responses, there is also some evidence that exaggerated blood pressure responses to mental stress may be a predictor of ischemia and/or subsequent clinical cardiac events in patients with CAD.[3,10,11] In this regard, it has been suggested that exaggerated hemodynamic responses to stress may be implicated in the etiology or clinical expression of CAD.[12] Thus, in the present study, we assessed the prognostic value of mental stress-induced blood pressure responses and left ventricular wall motion abnormalities assessed either using echocardiography or radionuclide ventriculography (RNV) for future cardiac events in CAD patients with a prior history of exercise-inducible ischemia.

METHODS

Patient population: A follow-up study was conducted of 96 patients who had participated in 2 prior published studies[1,4] that assessed mental stress-induced ischemia in patients with CAD in a laboratory setting. Fifty-seven patients were studied at the University of Maryland at Baltimore, Maryland, and at the

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Georgetown University and Veterans Administration Medical Centers in Washington, DC, and had left ventricular wall motion studies using 2-dimensional echocardiography (referred to as the Echo group).[4,13] Another 39 patients were studied at Cedars-Sinai Medical Center in Los Angeles using RNV (referred to as the RNV group). Of 96 patients, 7 were lost to follow-up and 3 others died of unknown causes. Seven patients who underwent a revascularization procedure within 1 month of the initial study were excluded from the present prognostic analyses because referral for coronary artery bypass surgery or coronary angioplasty may have resulted in part from the stress testing information obtained in this study. The remaining 79 (3 women and 76 men; mean age 58 ±10 years; range 37 to 78) were followed for a median duration of 3.5 years (range 2.7 to 7.3). All 79 patients had CAD as confirmed by previous myocardial infarction or coronary angiography or a >90% probability of coronary disease determined by Bayesian analysis of age, gender, risk factors, and history or positive exercise test.[14] One of the 79 patients had uninterpretable exercise test results, and was therefore excluded from exercise test analyses. This study was approved by the relevant institutional review boards, and informed consent was obtained from all patients.

Test protocol: Before testing, β blockers were withheld for 48 hours, calcium antagonists for 24 hours, and long-acting nitrates were withheld on the morning of testing. As reported previously,[4] for the Echo group patients, regional wall motion was assessed using real-time 2-dimensional echocardiography, with studies performed with a phased-array ultrasonograph (Hewlett Packard or Sonos, Andover, Massachusetts). Images were digitized off-line using a Datavue II image analysis system (Microsonics, Indianapolis, Indiana).[13] RNV group patients were injected with technetium-99m in vitro–labeled blood cells. When imaging was performed with mental stress testing, the patients were positioned in a semierect position. R-wave synchronized, multiple-gated RNV was performed with the gamma camera positioned in the left anterior oblique angle. Left ventricular wall motion was determined at each rest and intervention.

Baseline period: Testing sessions began with a rest period of at least 15 minutes, during which patients were encouraged to relax. At the end of the rest period, baseline wall motion and hemodynamics were obtained. Electrocardiogram, heart rate, and blood pressure were recorded every 2 minutes during the last 10 minutes.

Mental stress testing: Patients performed two 5-minute mental stress tasks, public speaking and mental arithmetic, separated by a rest period. RNV group patients also performed the Stroop color-word task and read a neutral passage aloud; these data are not included here to allow comparisons of Echo and RNV group data in the current analyses. For the public speaking task, patients delivered a 5-minute speech about their undesirable habits to examiners. During mental arithmetic, the patient was instructed to count backwards by 7 from a 4-digit number while being urged to count faster and more accurately.

Left ventricular wall motion images were acquired at the end of each rest phase and during each stressor. Electrocardiogram and heart rate were monitored continuously while blood pressure was recorded by an automatic cuff every 2 minutes. Peak blood pressure response to either of the mental stress tasks was quantified.

Exercise testing: Exercise testing followed the mental stress tasks. After preexercise baseline images, patients exercised on an upright bicycle. Exercise workload was increased by 150 to 200 kpm every 3 minutes until the test was stopped because of fatigue, marked chest pain, or severe electrocardiographic abnormality. Blood pressure was measured manually every 3 minutes, and the electrocardiogram continuously monitored for ST-segment depression and heart rate. Echo group patients underwent echocardiographic imaging during and immediately after exercise, RNV group patients were assessed for wall motion during the last 2 minutes of each exercise stage, and immediately after exercise. Ischemic ST-segment depression was defined as horizontal or downsloping depression of 1 mm (1.5-mm upsloping depression), below baseline, at 0.08 second after the J point.

Assessment of left ventricular wall motion: echocardiography (echo group): During 2-dimensional echocardiography (echo group), 16 segments were scored by experienced observers blind to the patient's clinical data. Each segment was rated on a 4-point scale: 1 = normal motion or hyperkinesia, 2 = hypokinesia (<5-mm inward excursion); 3 = akinesia, and 4 = dyskinesia. Dividing the sum of the scores by the number of segments yielded an average wall motion score. Intraobserver reliability of wall motion scores in our laboratory is good (coefficient of correlation 0.84), with an inter-reader measurement error of 0.146.[4,15,16] A change in wall motion score of >0.15 is therefore considered significant. Ejection fraction changes to mental stress and exercise were not calculated for echo group patients in the present sample, and analyses are therefore not presented for this variable.

Radionuclide ventriculography (RNV group): Wall motion was assessed in RNV group patients by experienced observers blind to clinical data, as described previously.[1,11] A score was assigned to each of 5 ventricular segments using the following classification system: 3 = normal motion, 2 = mild hypokinesia, 1 = moderate to severe hypokinesia, 0 = akinesia, and −1 = dyskinesia.[17] Wall motion was considered worsened when the score decreased by at least 1 from both baseline and the immediately preceding score.

Quantification of high versus low hemodynamic responding: Because peak hemodynamic values were quantified previously for the RNV group, maximal (peak) changes in blood pressure and heart rate during mental stress are reported for the mental stressors. For computing peak changes, the highest response obtained during either of the 2 stressors was used. To assure that a high stress-responding group was iden-

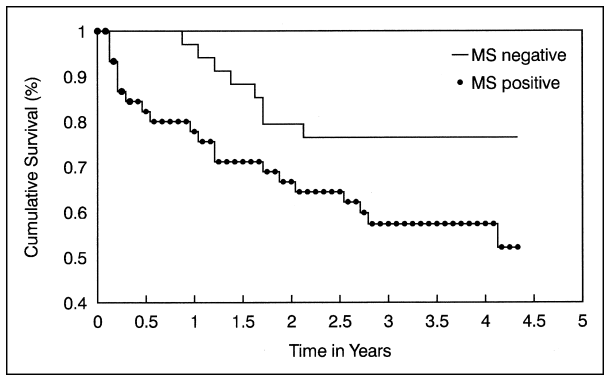

FIGURE 1. Occurrence of new cardiac events over time during 4.4-year follow-up period (median duration 3.5 years) as a function of whether patients evidenced mental stress-induced ischemia (MS positive) or no mental stress ischemia (MS negative) at initial testing. Differences between MS-positive and MS-negative patients over time was p = 0.048.

tified, high hemodynamic stress responding was defined as the upper third of peak diastolic blood pressure, systolic blood pressure, or heart rate change to either mental stress task. Low responders were defined as the lower two thirds in responding.

Follow-up: Patients, or in the case of deceased subjects, a member of their immediate family, were interviewed by telephone about new cardiac events, defined as new coronary angioplasty, coronary artery bypass surgery, nonfatal myocardial infarction, or cardiac death. Death was classified as either cardiac or noncardiac in origin, and clinical status was confirmed by the patient's treating physician in 54 of 79 cases. The median follow-up duration was 3.5 years (range 2.7 to 7.3).

Statistical analyses: Continuous variables are displayed as mean ± SD and *t* tests or analysis of variance were used when appropriate. Chi-square tests were used to evaluate frequencies or dichotomous data. Hemodynamic changes from rest to peak mental stress were analyzed using repeated-measures analysis of variance. Relative risks were calculated using odds ratios, and multivariate analyses were conducted using Cox regression. The occurrence of events during the course of follow-up was examined using the Kaplan-Meier curve and tested with the Breslow statistic.[18,19] All data were censored at a maximum of 4.4 years (20% of subjects were still available at that time). The p values <0.05 (2-tailed) were used as a cutoff for statistical significance unless otherwise indicated.

RESULTS

Mental stress-induced and exercise-induced ischemia: frequency and patient characteristics: New or worsened left ventricular wall motion abnormalities indicative of ischemia occurred in 61 patients (77%) during exercise. Mental stress-induced ischemia occurred in 45 patients (57%), of whom nearly all (n = 43) were exercise positive. There was an equivalent frequency of exercise-inducible ischemia (79% vs 75%, respectively) and mental stress ischemia (57% vs 56%, respectively) among echo and RNV group patients. In the combined samples, ischemia was more often provoked by speech (n = 39; 49%) than by mental arithmetic (n = 28, 35%; $p<0.05$).

Patients with mental stress-inducible ischemia did not differ significantly from patients without mental stress ischemia in demographics or cardiovascular risk factors, including age, family history of CAD, serum cholesterol levels, and history of smoking or hypertension.

Frequency and prediction of new cardiac events: Twenty-eight cardiac events occurred during follow-up. These included 5 cardiac deaths, 9 myocardial infarctions, 9 coronary artery bypass surgeries, and 5 angioplasties. Kaplan-Meier survival analysis (Figure 1) indicated that patients with mental stress ischemia experienced new cardiac events more frequently than those without mental stress ischemia, a trend maintained throughout follow-up (p = 0.048). New cardiac events occurred during follow-up in 20 patients with (44%) and in 8 without (23.5%) mental stress ischemia (odd ratio [OR] 2.60, 95% confidence interval [CI] 0.97 to 6.97; p = 0.057). Figure 2 presents the breakdown of cardiac events according to mental stress positive or negative status. The type of event was similarly distributed among the 2 groups.

Of patients who were positive for exercise-induced ischemia, 23 of 61 (37.7%) experienced new cardiac events compared with exercise-negative patients, of whom 5 of 17 (29.4%) had new events (OR 1.45, CI 0.45 to 4.66; p = NS).

Hemodynamic mental stress responses and prediction of new events: A comparison between the echo and RNV groups on mean hemodynamic changes revealed significant group differences in systolic blood pressure responses during mental stress, with peak systolic blood pressure increasing higher in the echo versus RNV group (49 ± 20 vs 36 ± 15 mm Hg; p = 0.005), perhaps due to center differences in patients stress test administration or patient demographics. Also, the peak heart rate response was higher in the echo group (36 ± 22 vs 18 ± 13 beats/min). Therefore, risk ratios for new events associated with hemodynamic responses were adjusted for group status.

Kaplan-Meier survival analysis (Figure 3) revealed that patients in the highest third of diastolic blood pressure responses experienced new cardiac events sooner and at a higher rate than the remaining patients who had smaller diastolic blood pressure stress responses (p = 0.053). After controlling for baseline diastolic blood pressure and group status, there was a significantly higher relative risk for high versus low stress-induced peak diastolic blood pressure responses (RR = 2.40, CI 1.10 to 5.20; p = 0.03). New events occurred in 50% (12 of 24) of the high diastolic blood pressure responders, compared with 28% (14 of 50) of the remaining patients (p = 0.03; Figure 4). Similar analyses of heart rate and systolic blood pressure changes to stress did not reveal significant associations with cardiac events.

To assess whether the predictive contribution of

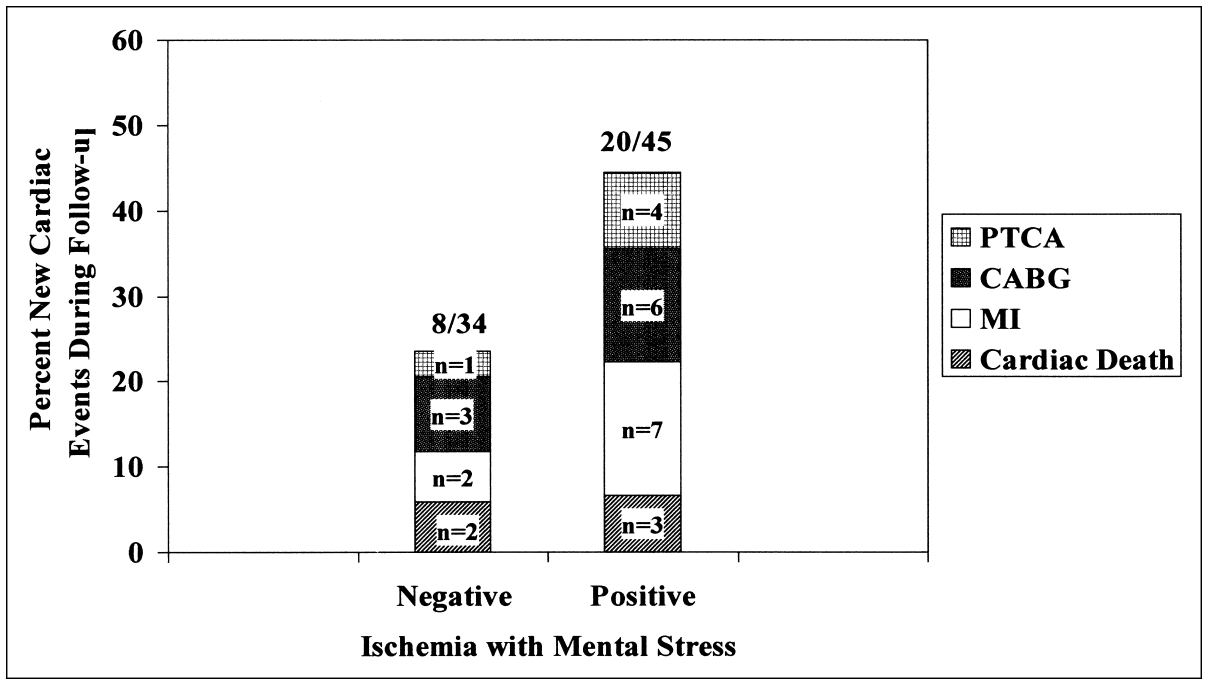

FIGURE 2. Number and type *(cross-hatching)* of new cardiac events occurring during median follow-up of 3.5 years as a function of presence (Positive) versus absence (Negative) of mental stress-induced ischemic wall motion abnormalities at initial testing. Patients with mental stress ischemia were more likely to experience cardiac events during follow-up (44% vs 24%; p <0.06). CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

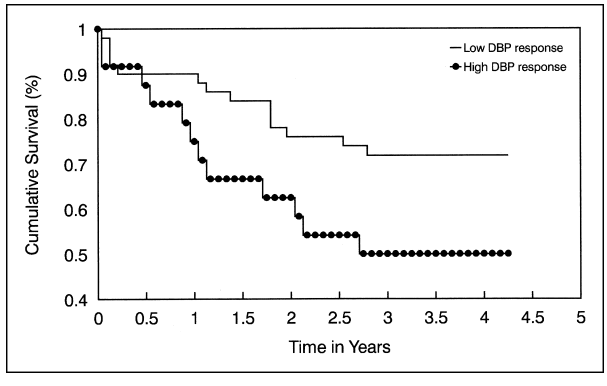

FIGURE 3. Occurrence of new cardiac events over time during 4.4-year follow-up period (median duration 3.5 years) as a function of whether patients demonstrated high *(upper third)* versus low *(remaining two thirds)* peak diastolic blood pressure (DBP) responses to either stressor during mental stress testing. Differences between high and lower DBP responders over time was p = 0.053.

diastolic blood pressure responsiveness was independent of the presence of mental stress ischemia and baseline diastolic blood pressure, a multivariate Cox regression model was conducted. This analysis first entered group status (echo or RNV) and baseline diastolic pressure into the model. Baseline diastolic blood pressure did not contribute to new events (p = 0.62). Ischemia during mental stress ischemia and peak diastolic blood pressure responses both made a modest contribution (both p = 0.10), with relative risks of 2.13 (CI 0.87 to 5.22) and 1.95 (CI 0.88 to 4.36), respectively. Thus, it appears that mental stress ischemia and blood pressure responses were roughly comparable in predicting cardiac outcomes.

DISCUSSION

This study demonstrates that mental stress-inducible ischemia, measured in terms of the presence of new wall motion abnormalities during echocardiography or RNV, is associated with a more than twofold risk of subsequent cardiac events when compared to patients without mental stress ischemia. This result agrees with the results of similar studies[8,9] reporting associations between ejection fraction measures of ischemia with mental stress and subsequent cardiac outcomes. In addition, we noted that a high level of diastolic blood pressure responses to stress was also predictive of subsequent events in this group. Collectively, these data suggest that measures derived from mental stress testing, including ischemic responses and peak diastolic blood pressures responses, may be useful in assessing prognosis in CAD patients with prior history of positive exercise tests.

Similar to 2 prior studies,[8,9] we observed few, if any, demographic, clinical, or risk factor variables differentiated between patients with and without cardiac events, or between mental stress-positive and stress-negative groups. Thus, it is unlikely that the predictive value of mental stress testing for cardiac events is attributable to standard risk factors, although we cannot rule out the possibility that revascularization procedures may have been prompted by the results of mental stress testing. One of the mechanisms underlying the predictive value of mental stress testing in this and prior studies may include a greater isch-

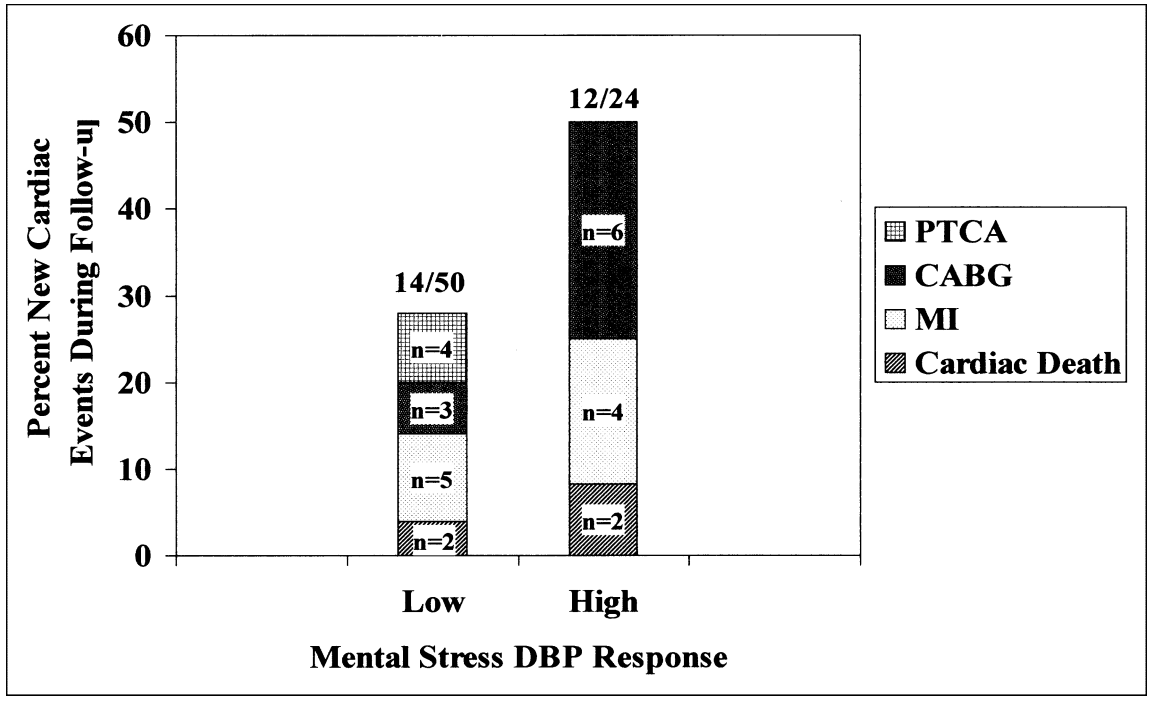

FIGURE 4. Number and type *(cross-hatching)* of new cardiac events occurring during median 3.5-year follow-up period as a function of high versus lower peak diastolic blood pressure (DBP) responses during initial mental stress testing. Patients with high peak DBP responses were more likely to experience cardiac events during follow-up than the remaining patients with low peak DBP responses (50% vs 28%; p <0.03). Abbreviations as in Figure 2.

emic burden during activities of daily life, which may be predictive of poorer prognosis in stable CAD patients.[20,21] Previous research has indicated that patients with mental stress ischemia in the laboratory exhibit more daily life ischemia during ambulatory monitoring,[3,4,22] particularly during sedentary daily activities.[4] One reason is that mental stress-positive patients may also have ischemia that is provokable during a wider range of daily activities. For example, Gottdiener et al[4] showed that patients with inducible ischemia to a wider range of mental stressors had a lower threshold for exercise-induced ischemia. Rozanski et al[1] demonstrated a negative correlation between the threshold for exercise-induced ischemia and the extent and severity of mental stress-induced ischemia; however, this has not been a consistent finding.[23]

A second mechanism by which mental stress testing is predictive of events may be related to heightened hemodynamic responsiveness among patients with mental stress-induced ischemia. Previous studies have also shown that enhanced blood pressure responsiveness to mental stress is also related to ischemia during daily life.[3] The present data are also consistent with the hypothesis that increased hemodynamic responsiveness to stress is a marker of risk for subsequent cardiac events in patients with CAD.

One of the underlying mechanisms by which mental stress induces myocardial ischemia in susceptible patients[1,24] is coronary vasoconstriction.[25,26] It has been proposed[8] that it is the vasoconstrictive effects of catecholamines released during mental stress that result in the left ventricular wall motion abnormalities observed during mental stress ischemia, thus lending support to a role for a mechanism involving reduced supply. In this regard, a role for increased systemic vascular resistance in mental stress-induced ischemia has been noted.[3,27]

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