

Relationship Among Mental Stress–Induced Ischemia and Ischemia During Daily Life and During Exercise: The Psychophysiologic Investigations of Myocardial Ischemia (PIMI) Study

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- OBJECTIVES** The purposes of this database study were to determine: 1) the relationship between mental stress–induced ischemia and ischemia during daily life and during exercise; 2) whether patients who exhibited daily life ischemia experienced greater hemodynamic and catecholamine responses to mental or physical stress than patients who did not exhibit daily life ischemia, and 3) whether patients who experienced daily life ischemia could be identified on the basis of laboratory–induced ischemia using mental or exercise stress testing.
- BACKGROUND** The relationships between mental stress–induced ischemia in the laboratory and ischemia during daily life and during exercise are unclear.
- METHODS** One hundred ninety–six stable patients with documented coronary disease and a positive exercise test underwent mental stress testing and bicycle exercise testing. Radionuclide ventriculography and electrocardiographic (ECG) monitoring were performed during the mental stress and bicycle tests. Patients underwent 48 h of ambulatory ECG monitoring. Hemodynamic and catecholamine responses were obtained during mental stress and bicycle tests.
- RESULTS** Ischemia (reversible left ventricular dysfunction or ST segment depression ≥ 1 mm) developed in 106 of 183 patients (58%) during the mental stress test. There were no significant differences in clinical characteristics of patients with, compared with those without, mental stress–induced ischemia. Patients with mental stress ischemia more often had daily life ischemia than patients without mental stress ischemia, but their exercise tests were similar. Patients with daily life ischemia had higher ejection fraction and cardiac output, and lower systemic vascular resistance during mental stress than patients without daily life ischemia. Blood pressure and catecholamine levels at rest and during the mental stress tests were not different in patients with, compared with those without, daily life ischemia. Patients with daily life ischemia had a higher ejection fraction at rest and at peak bicycle exercise compared with patients without daily life ischemia, but there were no other differences in peak hemodynamic or catecholamine responses to exercise. The presence of ST segment depression during routine daily activities was best predicted by ST segment depression during mental or bicycle exercise stress, although ST segment depression was rare during mental stress.
- CONCLUSIONS** Patients with daily life ischemia exhibit a heightened generalized response to mental stress. ST segment depression in response to mental or exercise stress is more predictive of ST segment depression during routine daily activities than other laboratory–based ischemic markers. Therapeutic management strategies might therefore focus on patients with these physiologic responses to stress and on whether lessening such responses reduces ischemia. (J Am Coll Cardiol 1999;33:1476–84) © 1999 by the American College of Cardiology

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Abbreviations and Acronyms

AECG	= ambulatory electrocardiographic
BP	= blood pressure
CAD	= coronary artery disease
CO	= cardiac output
ECG	= electrocardiographic
EDV	= end-diastolic volume
EF	= ejection fraction
ESV	= end-systolic volume
ETT	= exercise treadmill test
HR	= heart rate
kpm	= kilo pond meters
LV	= left ventricular
MI	= myocardial infarction
PIMI	= Psychophysiological Investigations of Myocardial Ischemia
RPP	= rate-pressure product
RVG	= radionuclide ventriculography
SV	= stroke volume
SVR	= systemic vascular resistance

Mental stress is known to precipitate episodes of myocardial ischemia in a subset of coronary patients (1-6), and has been implicated as a trigger of myocardial infarction (MI) and sudden death in patients with coronary artery disease (CAD) (7-11). Laboratory studies evaluating the relationship of mental stress and myocardial ischemia have employed a variety of markers to indicate the presence of ischemia, including reversible abnormalities of left ventricular wall motion, reductions in myocardial perfusion, ST segment depression and coronary vasoconstriction (1,2,4,5,12-15), and suggest that mental stress can trigger ischemia in 40% to 70% of stable CAD patients.

Whether common mechanisms are responsible for mental stress-induced ischemia and ischemia occurring during routine daily life activities and during exercise testing is unknown. Prior studies have assessed heart rate (HR) and blood pressure (BP) responses to mental stress (3,16) and the relationships between mental stress-induced ischemia in the laboratory and ischemia during routine daily life activities (4,16-18), but have not assessed the relative contributions of ejection fraction (EF), cardiac output (CO) and systemic vascular resistance (SVR), nor the responses of epinephrine and norepinephrine. Identification of the responsible mechanism(s) may have important implications for selection of optimal anti-ischemic medication (19).

The Psychophysiological Investigations of Myocardial Ischemia (PIMI) Study was a multicenter clinical investigation sponsored by the National Heart, Lung and Blood Institute designed to investigate the effects of mental stress in patients with stable CAD and to determine the psychologic, demographic and medical characteristics of patients who manifested myocardial ischemia in response to mental stress compared with those who did not. All patients underwent mental stress, exercise treadmill and bicycle testing in the laboratory and ambulatory electrocardiographic (AECG)

monitoring during routine daily life activities. The purposes of this report are to investigate 1) the relationship between mental stress-induced ischemia, ischemia during daily life activities and ischemia during exercise; 2) whether patients who exhibited ischemia during daily life experienced greater hemodynamic and catecholamine responses to mental or physical stress than patients who did not exhibit daily life ischemia, and 3) whether patients who experienced daily life ischemia could be predicted on the basis of laboratory-induced ischemia using mental or exercise stress.

METHODS

The PIMI study design and patient characteristics have been described previously (20). In brief, patients were eligible for inclusion if they had all of the following: 1) documented CAD; 2) evidence of myocardial ischemia, defined as ST segment depression ≥ 1.0 mm on an Asymptomatic Cardiac Ischemia Pilot protocol exercise treadmill test (ETT) conducted off anti-ischemic medications; 3) 48-h AECG monitoring conducted off medications; and 4) consent to participate. Patients were excluded for any of the following: pregnancy; MI within three months of qualifying ETT; percutaneous transluminal coronary angioplasty within six months of qualifying ETT; cardiac surgery requiring thoracotomy; unstable angina within four weeks of qualifying ETT; serious noncardiac illness (e.g., renal, pulmonary); inability to discontinue anti-ischemic and other specified medications; neurologic disease, and electrocardiographic (ECG) findings which would interfere with interpretation of the AECG (baseline ST segment deviation ≥ 1.0 mm or ECG evidence of left ventricular hypertrophy).

Patients who consented to participate and satisfied eligibility criteria were withdrawn from anti-ischemic medications and underwent a qualifying ETT and 48-h AECG, a bicycle exercise test with radionuclide ventriculography (RVG) and mental stress testing. Medications must have been stopped before PIMI testing according to the following rules: calcium channel blocking agents discontinued for at least three days; beta-adrenergic blocking agents discontinued for at least three days or five half-lives, whichever was longer, and long-acting nitrates discontinued for at least 12 h. These procedures occurred on three separate visits, several weeks apart. The exercise tests and mental stress tests were performed in the morning in a controlled and consistent environment.

Ambulatory ECG monitoring. Forty-eight-hour AECG recordings were performed using Applied Cardiac Systems AM cassette recorders (Laguna Beach, California). Electrodes were applied to reproduce the two ECG leads showing the greatest ST segment deviation during the ETT. The recordings were analyzed in the PIMI AECG Core Laboratory at the Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (21,22). An ischemic episode was defined as transient ischemic ST

segment deviation ≥ 1.0 mm lasting ≥ 1.0 min. In data analysis the number of ischemic episodes and cumulative duration of ischemia were divided by the actual length of recording to adjust for variations in recording time from a 48-h monitoring period.

Exercise testing. Symptom-limited ETTs were performed according to the Asymptomatic Cardiac Ischemia Pilot protocol (23) using standard criteria for stopping. The 12-lead ECG was acquired in the standing position before exercise, at each minute during exercise, at peak exertion and each minute after exertion until exercise-induced ST segment changes resolved. Heart rate and BP were recorded during each exercise stage and for each minute of recovery.

Bicycle ergometry was performed with the participant seated in a semiupright position, and a RVG (2-min acquisition time) was recorded with the 40° left anterior oblique view. Symptom-limited exercise commenced at a workload of 200 kilo pond meters (kpm) and increased every 3 min by 200 kpm to tolerance. Electrocardiograms and BP were recorded at rest and at 1-min intervals, and AECG was performed continuously during exercise. Blood samples for catecholamine determinations were drawn from an indwelling catheter at rest, at 1 min, and at the peak of exercise. Radionuclide ventriculograms were obtained at baseline and at each stage of exercise.

The exercise ECGs were processed at the PIMI ECG Core Laboratory at Saint Louis University as previously described (24,25). An abnormal exercise ECG lead was defined as: 1) J point and ST 80 depression ≥ 1.0 mm and ST segment horizontal or downsloping < 10 mm/s, or 2) ST 80 depression ≥ 1.5 mm and ST segment upsloping > 10 mm/s, as compared with the rest tracing. Time to onset of ischemic ST segment depression was determined when any lead (excluding aVR) met criteria for abnormality.

Mental stress testing. Mental stress testing consisted of a Speech test and a Stroop Color-Word test, each for 5 min, administered in random order, with two 2-min RVG images acquired during each test. For the Speech test, patients role-played presenting a complaint to a nursing home staff about inadequate care given to a close relative. The patient was asked to spend 1 min planning a response, then 5 min speaking while being observed and "evaluated" by laboratory staff. The Stroop test was administered by computer on a video monitor. A word appeared in the middle of the screen—RED, GREEN or BLUE—in one of these three colors. At the bottom of the screen the words RED, GREEN and BLUE appeared with the font color not matching the word meaning. The participant was asked to match the color of the word in the middle of the screen with the meaning of the color word at the bottom by pressing the appropriate mouse key. The display changed quickly, forcing the subject to make rapid selections in the face of confusing information. This computerized version of the Stroop test provided standardized administration and

automatic titration of difficulty based on level of performance. Blood specimens for neurohormones were drawn from an indwelling catheter after a rest period, 1 min after beginning each mental stress task, at the end of each task and 10 min after completing both. Blood pressure and HR were automatically recorded at 30 s after beginning each mental stress test and each minute thereafter. Radionuclide images were acquired for 2 min, beginning at 30 s and again at 3 min after initiating each stress task. The ECG was recorded during mental stress testing using an AECG recorder.

Radionuclide ventriculography. The procedure for obtaining and analyzing RVG images has been previously described (26). Radionuclide images were read at the PIMI Radionuclide Core Laboratory at Johns Hopkins University, Baltimore, Maryland. Regional wall motion was scored subjectively for each RVG using a four-point scale for each of four predefined segments. Calculation of left ventricular (LV) volumes was performed by validated methods (27). The LV end-diastolic volume (EDV) was obtained from the ratio of the attenuation-corrected end-diastolic count rate to the count rate per milliliter from a venous blood sample obtained in each subject. End-systolic volume (ESV) was calculated from the measured EF and EDV. Stroke volume (SV) was calculated as the difference between EDV and ESV, and CO was the product of SV and HR measured during RVG.

Rate-pressure product (RPP) was calculated as systolic BP \times HR. Mean arterial pressure was calculated as (systolic BP + 2 \times diastolic BP)/3. Total systemic vascular resistance (SVR) in dyn/s/cm^{-5} was calculated as mean arterial pressure \times 80/CO.

Definitions of ischemia. Patients were considered to have ischemia during a mental stress or exercise task in the laboratory if they met one or more of these three criteria: 1) ECG: ≥ 1 mm ST segment depression; 2) AECG: ≥ 1 mm ST segment depression lasting ≥ 1 min, and 3) RVG: a) during bicycle exercise test, new or worsening wall motion abnormality during stress or EF did not increase by $\geq 5\%$; or b) during mental stress, new or worsening wall motion abnormality during a task or EF decreased by $> 8\%$.

Both the EF criterion and the wall motion criterion for mental stress ischemia were determined after review of EF responses to the Speech and Stroop tests in a sample of 29 subjects without evidence of coronary disease by clinical history or exercise ECG (26).

History of angina during the preceding three months was determined from the Rose questionnaire (28).

Statistical methods. Differences between patients with and without ischemia in response to tests were performed using chi-square tests for categorical variables and the normal scores rank test (29) for continuous measures. Differences in mean values for characteristics of ischemic episodes detected during AECG (e.g., peak HR, maximum ST segment

Table 1. Patient Characteristics by Presence of Electrocardiographic, Ambulatory Electrocardiographic or Radionuclide Ventriculography Evidence of Mental Stress Ischemia

Characteristic	No Ischemia During Mental Stress (n = 106)		Ischemia During Mental Stress (n = 77)		P Value
	n	%	n	%	
Characteristic					
Male gender	94	88.7	63	81.8	0.19
Current smoker	19	17.9	11	14.3	0.51
Ever smoked	81	76.4	56	72.7	0.57
Age (yr, mean ± SD)	62.2 ± 3.4		63.5 ± 8.1		0.33
History					
Myocardial infarction	44	41.5	34	44.2	0.72
Congestive heart failure	2	1.9	4	5.2	0.24
Hypertension	47	44.3	41	53.2	0.23
Diabetes	14	13.2	14	18.2	0.36

depression) between patients with versus without mental stress-induced ischemia were tested using the generalized estimating equations method (30) to take account of the correlations among repeated ischemic episodes in the same patient. P values ≤0.05 were considered evidence of association. All analyses were performed using the SAS (Cary, North Carolina) software package (31,32).

RESULTS

Patient characteristics. One hundred ninety-six patients were enrolled, of whom 183 (93%) had data on the presence or absence of mental stress ischemia, and 189 (96%) had data on the presence or absence of ischemia during bicycle exercise. The patient characteristics have been described previously (20). In brief, the mean age was 63 years (range 41 to 80), 87% of the 196 patients were male, 87% were white, 74% had a history of cigarette smoking, 47% had a history of hypertension, 15% had a history of diabetes mellitus, 42% had a history of prior MI, 35% had a history

of prior angioplasty and 33% had a history of angina pectoris during the preceding three months.

Classification of patients who exhibited mental stress-induced ischemia. During the Speech test, 77 patients (42%) developed ischemia, 64 patients (35%) developed ischemia in response to the Stroop test and 106 patients (58%) developed ischemia to either test. There were no significant differences in clinical characteristics of patients with, compared with those without, mental stress-induced ischemia (Table 1).

Characteristics of daily life ischemia in patients with versus those without mental stress-induced ischemia. Patients who experienced mental stress ischemia in response to the Speech test tended to have a higher prevalence of AECG ischemic episodes, more ischemic episodes per 24 h and longer periods of ischemia per 24 h, compared with patients without mental stress ischemia. There was no difference in daily life ischemia based on responses to the Stroop test or to a combination of either test (Table 2).

Table 2. Ambulatory Electrocardiogram (AECG) and Exercise Treadmill Test (ETT) Findings by Presence of Mental Stress Ischemia

	Speech Test			Stroop Test			Either Speech or Stroop		
	Ischemia (n = 77)	No Ischemia (n = 106)	p	Ischemia (n = 64)	No Ischemia (n = 120)	p	Ischemia (n = 106)	No Ischemia (n = 77)	p
AECG findings									
Ischemic episodes/24 h	1.8 ± 3.2	1.1 ± 2.3	0.06	1.5 ± 3.4	1.4 ± 2.4	0.35	1.5 ± 2.9	1.3 ± 2.6	0.63
Minutes of ischemia/24 h	18.7 ± 39.8	8.0 ± 19.5	0.04	15.1 ± 35.7	11.9 ± 27.3	0.31	15.5 ± 35.7	8.9 ± 21.5	0.45
% patients with ischemia	49.4	34.9	0.05	35.9	45.8	0.20	43.4	39.0	0.55
ETT findings									
Total minutes of exercise	7.2 ± 2.6	7.7 ± 2.7	0.20	7.4 ± 2.5	7.8 ± 2.9	0.48	7.9 ± 2.7	7.3 ± 2.7	0.18
Minutes to onset of STD	5.0 ± 2.3	5.4 ± 2.4	0.34	5.0 ± 2.2	5.4 ± 2.6	0.39	5.5 ± 2.5	5.0 ± 2.3	0.17
Maximum STD (mm)	2.0 ± 0.6	2.0 ± 0.6	0.61	2.0 ± 0.7	2.0 ± 0.6	0.22	2.0 ± 0.6	2.0 ± 0.6	0.77
RPP at STD onset (×10 ³)	19.8 ± 4.6	16.6 ± 4.7	0.73	19.6 ± 4.3	19.6 ± 4.8	0.99	19.8 ± 4.9	10.5 ± 4.4	0.72

RPP = rate-pressure product; STD = ST segment depression.

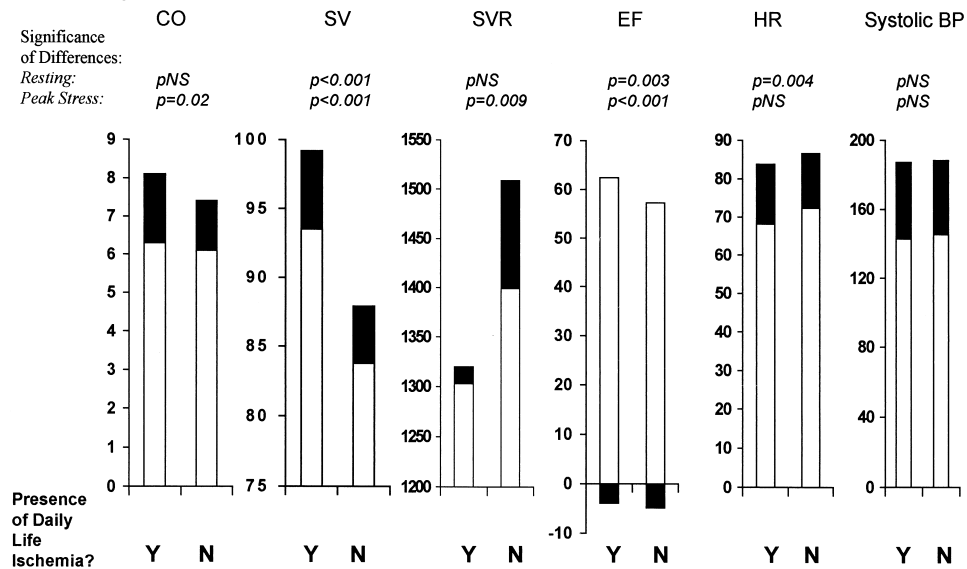


Figure 1. Hemodynamic responses during the Speech test in the 82 patients who experienced ischemia during routine daily activities and the 189 patients without ambulatory electrocardiographic ischemia. For each hemodynamic variable the values are shown for patients who experienced daily life ischemia (Y) and those who did not (N). The **open area** of each bar represents the value at rest and the **dark area** of each bar represents the change during the mental stress. BP = blood pressure (mm Hg); CO = cardiac output (liters/min); EF = ejection fraction (%); HR = heart rate (bpm); SV = stroke volume (ml/beat); SVR = systemic vascular resistance (dyn/s/cm³). P values <0.10 are reported; p values ≥0.10 are noted as pNS.

Characteristics of exercise-induced ischemia in patients with versus those without mental stress-induced ischemia. There were no significant differences in any characteristic of exercise-induced ischemia in patients with or without mental stress-induced ischemia, whether in response to the Speech or the Stroop test (Table 2).

The HR and the RPP at the onset of ischemia during the ETT was compared with the maximum HR and RPP during mental stress for patients with mental stress ischemia. The maximum HR (87.6 ± 15.8 beats/min) and RPP (17,034 ± 4,670) during mental stress were lower than the HR and RPP at the onset of ischemia during the ETT (129.1 ± 19.1 beats/min, 23,127 ± 5,454, respectively, p < 0.001).

Associations between hemodynamic and catecholamine responses during mental stress and the development of AECG ischemia. We have previously reported that patients who developed mental stress-induced ischemia experienced a more exaggerated increase in HR, BP, EDV, ESV and SVR in response to mental stress, compared with patients who did not develop ischemia, although there were no differences in epinephrine or norepinephrine levels (33). To evaluate whether the nature and magnitude of the physiologic response to mental stress identified those patients who experienced AECG ischemia during daily life activities for this database study, we compared the hemodynamics and catecholamine responses to mental stress in the 82 patients (43%) who experienced AECG ischemia with those of the 109 patients (57%) who did not (Fig. 1).

Compared with patients without AECG ischemia, those with AECG ischemia had higher EF and SV, and lower HR at rest before mental stress and higher EF, SV and CO, and lower SVR during the Speech test (Fig. 1). In contrast, the hemodynamic responses to the Stroop test were significantly less than those in response to the Speech test, as we have previously reported (33), and the Stroop responses were not substantially associated with the presence of ischemia. Blood pressure and catecholamine levels at rest and during the Speech or Stroop test were not associated with the presence of AECG ischemia.

Associations between hemodynamic and catecholamine responses during bicycle exercise stress and AECG ischemia. We also previously reported that patients who developed bicycle exercise-induced ischemia exhibited higher epinephrine and norepinephrine levels in response to exercise compared with patients who did not develop ischemia, associated with greater increase in ESV and EDV and smaller increase in SV and CO (33). For this database study we evaluated whether the nature and magnitude of hemodynamic and catecholamine responses to exercise were different in those patients with AECG ischemia and those without AECG ischemia. Patients who experienced AECG ischemia had a higher EF at rest and at peak bicycle exercise compared with patients without AECG ischemia (61.3 ± 11.1% vs. 56.9 ± 12.1% at rest, p = 0.01; 60.1 ± 11.6% vs. 55.8 ± 13.4% at peak exercise, p = 0.03), but there were no other significant associations between the presence of AECG ischemia and CO, SVR or catecholamine levels

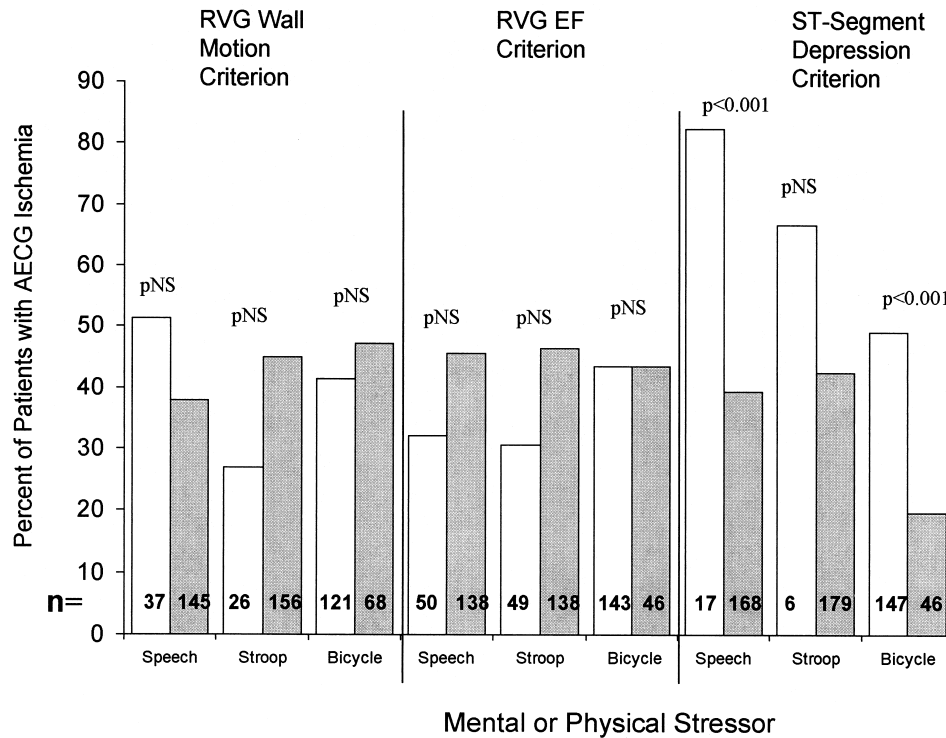


Figure 2. Frequency of ischemia on 48-h ambulatory electrocardiogram (AECG) by presence of criteria for ischemia induced by mental stress or bicycle exercise. Radionuclide ventriculography (RVG) wall motion criteria: 1) mental stress—new or worsened regional wall motion abnormalities during both mental stress images; 2) bicycle exercise—new or worsened regional wall motion abnormality during peak exercise image. Radionuclide ventriculography ejection fraction (EF) criteria: 1) mental stress—EF decrease >8%; 2) bicycle exercise—EF does not increase \geq 5%. ST segment depression criterion: mental stress or bicycle exercise— \geq 1 mm ST segment depression for \geq 1 min on AECG or \geq 1 mm ST segment depression on 12-lead electrocardiogram. n = number with criteria present during stress test. P values <0.10 are reported, p values \geq 0.10 are noted as pNS. **Open bars** = ischemia; **shaded bars** = no ischemia.

(data not shown) at rest or at peak exercise, other than slightly smaller SVR at peak exercise in those with daily life ischemia than in those without (982 ± 253 vs. 1093 ± 347 dyn/s/cm⁻⁵, p = 0.04).

Prediction of patients who develop ischemia during daily life based on laboratory-induced markers of ischemia.

The only laboratory marker of ischemia that identified patients who developed AECG ischemia during daily life was the development of ST segment depression during the Speech test or during bicycle exercise (Fig. 2). Although few patients (17 patients, or 9.2%) had ST segment deviation during the Speech test, 82% of these patients developed daily life ischemia. This compares with 39% of patients exhibiting daily life ischemia among the 168 patients who did not develop ST segment depression during mental stress (p < 0.001). Of the 147 patients who developed bicycle exercise-induced ST segment depression, 49% developed daily life ischemia, compared with only 20% of the 46 patients who did not develop exercise-induced ST segment depression (p < 0.001). In contrast to the predictive value of ST segment depression in the laboratory, the RVG criteria of ischemia (i.e., new or worsening wall motion abnormality or fall in EF) during mental or bicycle stress did not predict those patients who developed AECG ischemia.

DISCUSSION

Our study demonstrates that patients who exhibited mental stress ischemia manifested more episodes of ischemia during daily life activities than patients who did not exhibit mental stress ischemia. Patients who experience daily life ischemia appear to have heightened resting hemodynamics and a more exaggerated peak hemodynamic response to mental stress compared with patients without daily life ischemia, suggesting they are prone to excessive hemodynamic responses to mental stress. Exercise treadmill test performance was similar in patients who developed ischemia in response to mental stress compared with those who did not.

Our ability to predict patients likely to develop ischemia during daily life utilizing markers of ischemia in the laboratory was based entirely on the development of ST segment depression which occurred during either mental or exercise stress; LV wall motion responses to mental or exercise stress were not associated with an increased incidence of daily life ischemia.

Relationship between mental stress ischemia and daily life ischemia. Our study sheds light on why patients with mental stress ischemia were more likely to experience

AECG ischemia during daily life activities. The heightened resting hemodynamics and more exaggerated peak hemodynamic response to mental stress in patients who experience daily life ischemia suggest that they may be in a chronic state of increased sympathetic arousal, and more prone to an exaggerated sympathetic systemic response to mental or exercise stress as well. The HR at rest and in response to stress was lower in our patients with daily life ischemia compared with the patients without daily life ischemia, which may represent a reflex response to the chronically increased EF and SV. We found no correlation between the level of serum epinephrine or norepinephrine at rest or at peak stress and the presence or absence of daily life ischemia, but these may not be an adequate gauge of either a chronic or an acute state of arousal or associated vascular effects.

The strong association between the hemodynamic responses to the Speech test and the development of daily life ischemia (Fig. 1), and the lack of an association with responses to the Stroop test merit comment. The relationship between responses to the Stroop test and daily life ischemia was so weak that it actually eliminated the relationship between the Speech test and daily life ischemia when the analysis considered both mental stress tests combined (Table 2). The association with the Speech test and poor association with the Stroop test most likely represent the fact that the Speech test more closely approximates the kind of mental stresses that coronary patients deal with on a daily basis. The Stroop test may be too contrived a laboratory test to be representative of daily life stresses. These observations may be important for future studies utilizing laboratory tests of mental stress in coronary patients.

It is interesting that the hemodynamic "response profile" to mental stress which predicts the development of daily life ischemia (i.e., increased CO, SV and EF, and decreased SVR) is different than the "response profile" to mental stress which predicted the development of ischemia during mental stress in the laboratory (i.e., decreased CO, SV and EF, and increased SVR), which we have previously reported (33). These differences may reflect the heterogeneity of stressors and physiologic responses that may lead to the development of ischemia. Ischemia during daily life is accompanied by increased inotropy, but ischemia during mental stress in the laboratory is associated with peripheral vasoconstriction and increased afterload. We did not monitor hemodynamic variables during daily life to determine the variables responsible for ischemia in the ambulatory setting.

Relationship between mental stress ischemia and exercise-induced ischemia. There were no significant differences in any characteristic of treadmill exercise performance in patients with or without mental stress ischemia. Ischemia occurring during exercise is due primarily to generally equivalent increases in HR and BP required by the increase in metabolic demands. Ischemia occurring in re-

sponse to mental stress, in contrast, is associated with a less marked increase in HR or BP compared with exercise stress, and a significant increase in SVR (33), suggesting that coronary vasoconstriction may contribute to the development of mental stress ischemia. Our results indicated that the ischemia threshold (RPP at onset of ischemia) is lower during mental stress than exercise stress, underscoring the contribution of coronary vasoconstriction to mental stress ischemia. Because the mechanisms responsible for exercise-induced and mental stress-induced ischemia are, in part, different, it is not surprising that there may be no correlation between the two. The tests were also performed at different visits several weeks apart. The variability of mental stress-induced ischemia (34) may have also lessened the likelihood of observing a relationship with exercise-induced ischemia if one were present.

Prediction of daily life ischemia based on mental or exercise stress responses (ST segment depression, increase in EF or wall motion abnormalities) in the laboratory. The only laboratory marker of ischemia useful to identify patients who experience daily life ischemia by AECG monitoring was the development of ST segment depression during mental or exercise stress (Fig. 2). This marker occurred infrequently during mental stress (17 patients during the Speech test), although it occurred frequently during bicycle exercise stress (147 patients). However, over 80% of patients with ST segment depression during mental stress had daily life ischemia, whereas the percentage of patients with exercise-induced ischemia who had daily life ischemia was just under 50%. Thus, patients with mental stress-induced ST segment depression are likely to have daily life ischemia, and may be at increased risk for cardiac events (35,36), similar to patients with ST segment depression during exercise. These patients may be candidates for more aggressive intervention. Left ventricular wall motion abnormalities or changes in EF during exercise and mental stress did not predict those patients who experienced AECG ischemia. The significance of these observations is not clear. If ST segment depression is a less sensitive marker for detection of laboratory-induced ischemia than radionuclide methods, one might also expect this to be true during daily life. Episodes of mental stress-induced ischemia during daily life detected by AECG monitoring may be produced by more prolonged or intense episodes of mental stress than are practical or ethical to produce in the laboratory. More study is necessary to clarify the manifestations of myocardial ischemia observed during mental stress.

Limitations. In this report we evaluated the ischemic, hemodynamic and neurohumoral responses to exercise and mental stress in a number of clinical and laboratory settings. We utilized standard and convenient noninvasive definitions such as ST segment changes, the presence of a fall in EF ≥ 8 percentage units or worsening or new wall motion abnormalities. Although there is no certainty that these

definitions truly represent myocardial ischemia, these definitions were based on actual comparison with an age-matched reference group studied specifically for PIMI without clinical or exercise ECG evidence of coronary disease (26). The validity of the definitions of myocardial ischemia used in PIMI is supported by the results of a recent study which demonstrated that patients who experienced ischemia after mental stress, using similar definitions of ischemia, had a significantly worse cardiac prognosis than patients who did not develop mental stress ischemia (35).

The analyses comparing patients based on the presence or absence of AECG ischemia or mental stress ischemia may also be limited by the difficulty in identifying the presence of mental stress ischemia or daily life ischemia on the basis of a single laboratory visit or a single 48-h AECG. Susceptibility to mental stress ischemia is highly variable from day to day (34), as is ischemia during AECG monitoring (37).

Clinical implications. Psychophysiologic Investigations of Myocardial Ischemia is the largest study to focus on the characteristics of mental stress ischemia and the hemodynamic and neurohumoral responses to mental stress and to compare these variables in patients with versus those without daily life ischemia. Our study indicates that patients with daily life ischemia are those who have a heightened generalized response to mental stress. Since the presence of mental stress ischemia is associated with an adverse outcome (35,36), management strategies, therefore, may be focused on those patients who have exaggerated systemic physiologic responses to mental stress, with attention toward behavioral modification and pharmacologic intervention to prevent the excess physiologic response.

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