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Role of Behavioral and Psychological Factors in Mental Stress–Induced Silent Left Ventricular Dysfunction in Coronary Artery Disease

MATTHEW M. BURG, PHD,*† DIWAKAR JAIN, MD,† ROBERT SOUFER, MD, FACC,*†
ROBERT D. KERNS, PHD,*† BARRY L. ZARET, MD, FACC†

West Haven and New Haven, Connecticut

Objectives. **We examined the relationship of the psychological profile to left ventricular dysfunction induced during mental stress.**

Background. **The contribution of psychological factors to mental stress–provoked silent myocardial ischemia has not been explored.**

Methods. **Thirty patients with chronic stable coronary artery disease and a reversible defect on stress thallium-201 imaging completed a psychological assessment by questionnaire and Structured Interview, serially administered mental stress and brief walking exercise. Blood pressure, electrocardiogram (ECG) and left ventricular indexes were obtained by ambulatory serial radionuclide ventriculography. Silent ventricular dysfunction was defined by a decrease ≥0.05 in ejection fraction or ≥1 mm in ST segment on the ECG in the absence of symptoms.**

Results. **Of the 30 patients, 15 (Group I) had evidence of silent left ventricular dysfunction during mental arithmetic. The other 15 (Group II) showed no change. In addition, 18 of 30 patients had this dysfunction during the Structured Interview. Both ischemic and nonischemic groups developed comparable and significant increases in heart rate and blood pressure. Group I patients were distinguished by higher scores on measures of aggressive responding ($p < 0.001$), trait anger ($p < 0.0001$), hostile affect ($p < 0.003$) and an index of behavioral reactivity ($p < 0.003$) and a lower score on anger control ($p < 0.001$). No other variables, including historical and clinical indexes, discriminated between the two groups.**

Conclusions. **Patients with coronary artery disease and mental stress–provoked silent ventricular dysfunction were distinguished by a psychological profile consistent with emotional reactivity to social interaction and mental provocation, with anger as the predominant affective state. Patients with such a profile may be at risk of frequent silent left ventricular dysfunction.**

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In patients with known coronary artery disease, transient myocardial ischemia in the absence of symptoms is common during activities of daily life (1). This silent myocardial ischemia usually occurs at a relatively low rate-pressure product compared with that during exercise-induced ischemia (2–5), suggesting that the cause of the ischemia may not be solely an alteration in myocardial oxygen demand. Although somewhat controversial, the psychological profile has been proposed as a potential factor in this phenomenon (6). A profile characterized by hostility, anger and a pattern of behavior described by behavioral and emotional reactivity (type A [7]) has been associated with increased risk of myocardial infarction and sudden cardiac death (vs. angina) as the initial presentation of coronary artery disease (8,9). In addition, patients with coronary artery disease who have a profile characterized by these factors are found to ignore or underreport physical symptoms during the performance of challenging or provocative tasks and appear to be less likely than patients without this profile to experience angina during treadmill exercise testing (10–13). There is also an increasing awareness that mental and emotional stress can be potent provocateurs of silent ischemia (14–20), and individuals with this profile evidence greater responsivity to such provocation (21–25). Thus, the role of a psychological profile characterized by hostility, anger and behavioral reactivity in the manifestations of ischemic cardiac syndromes requires further investigation.

We sought to determine whether such a psychological profile plays a role in silent ischemia. Our hypothesis was that individuals who have evidence of silent ischemia during mental stress would be distinguished by a hostile, angry, type A response style and associated behavioral reactivity. To monitor for silent ischemia, we used a sensitive ambulatory radionuclide serial assessment of left ventricular function that was previously used in the study of coronary artery disease (26).

Methods

Study patients. Forty consecutive patients undergoing exercise or dipyridamole quantitative stress thallium-201

From the *Cardiovascular Behavioral Medicine Program, Cardiovascular Nuclear Medicine Service and Psychology Service, Veterans Affairs Medical Center, West Haven, Connecticut and the †Section of Cardiovascular Medicine, Departments of Internal Medicine and Psychiatry, Yale University School of Medicine, New Haven, Connecticut. This work was supported in part by a Merit Review grant to Drs. Burg and Soufer from the Department of Veterans Affairs, Washington, D.C.

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Address for correspondence: Matthew M. Burg, PhD, Health Psychology Section, 116 B 4, Veterans Affairs Medical Center, West Haven, Connecticut 06516.

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imaging because of suspected coronary artery disease and showing evidence of reversible myocardial ischemia (reversible thallium-201 defect and heart/lung thallium-201 uptake ratio consistent with ischemia) were selected for study; 30 agreed to participate. Those who declined participation did so because of travel distance to the medical center. All had a baseline left ventricular ejection fraction ≥0.40 and chronic stable coronary artery disease. Their mean age was 64 years (range 43 to 75). Thirteen had prior myocardial infarction; 12 had a history of hypertension, with blood pressure controlled in all at the time of study. Mean baseline left ventricular ejection fraction was 0.55 (range 0.43 to 0.67). Mean computerized stress thallium-201 defect score was 7.7, with a mean reversibility score of 3.8, which in our laboratory represents a moderate perfusion defect (27). Exclusion criteria included documented myocardial infarction within the past 3 months, coronary artery bypass graft surgery or coronary angioplasty within the last 6 months, valvular heart disease, uncontrolled cardiac arrhythmia, concurrent congestive heart failure or baseline left ventricular ejection fraction <0.40, insulin-dependent diabetes mellitus, age >75 years, new onset angina or a change in the anginal pattern of <4 weeks' duration, incapacitating or life-threatening concomitant illness, a history of treatment for psychotic disorder and a history of substance abuse. Patients continued their routine antianginal medication regimen throughout the study because prior work (19) has demonstrated little or no impact of these medications on mental stress–provoked ischemia. Nine patients were receiving beta-adrenergic blocking agents, 15 were receiving calcium antagonists and 4 were receiving long-acting nitrates either singly or in combination. Six were receiving no antianginal medication. No patients were receiving psychotropic medications.

Test protocol. The study was approved by the Human Investigation Committee at both the West Haven VA Medical Center and Yale University School of Medicine. It consisted of psychological assessment and serially administered laboratory tasks that were separated by 5-min rest periods. The laboratory protocol was preceded by a 20-min baseline stabilization period and followed by a 20-min post-protocol period. Psychological assessment consisted of take-home paper/pencil questionnaire battery and Videotaped Structured Interview (approximately 30 min); laboratory tasks included mental arithmetic and choice reaction time (5 min each). In addition, each subject performed mild walking exercise for approximately 10 min at the end of the laboratory protocol. During each of these tasks (with the exception of the questionnaire battery), left ventricular ejection fraction, relative ventricular volumes, ECG and heart rate were monitored; blood pressure was also monitored during all tasks except exercise. The total time for the laboratory protocol (including Structured Interview) was 105 ± 10 min. Testing was always performed between the hours of 1 PM and 3:30 PM, with patients reporting to the laboratory at noon on the test day. After obtaining informed consent, the patient's red blood cell pool was labeled with 20 to 25 mCi of technetium-99m using a standard technique (28). Equilibrium radionuclide angiocardiography at rest was obtained with a conventional gamma camera in the left anterior oblique view, from which baseline left ventricular ejection fraction was acquired.

Ambulatory serial radionuclide ventriculography. After gamma camera studies at rest were obtained, the ambulatory ventricular function monitor (VEST) was positioned on the chest in a standardized manner using gamma camera imaging (26,29). It was held in place by a semirigid plastic garment and a supporting mounting bracket. A second gamma camera study in the left anterior oblique view was obtained to ensure proper placement of the VEST detector.

The VEST device was recently developed for the study of silent myocardial ischemia (29–32). In brief, it continuously records a two-channel ECG (leads V_1 and V_5) and beat by beat left ventricular blood pool activity. The ECG-gated analysis of ejection fraction and relative end-diastolic and end-systolic volumes is accomplished off-line by a dedicated minicomputer, which provides a printout of these variables over the period of study.

Throughout the duration of the study, radionuclide data from the VEST, gated with the ECG, were recorded continuously and averaged over 30-s periods; heart rate, systolic and diastolic blood pressure and mean arterial pressure were sampled at 2-min intervals. Mean left ventricular ejection fraction was calculated for the last 4 min of baseline study and for each task period; heart rate and blood pressure were treated comparably. The ECG was analyzed for the presence of ST segment changes at any time during the study. Left ventricular dysfunction was defined by an absolute decrease ≥0.05 in ejection fraction from baseline to task lasting ≥2 min. Ischemia was defined by the presence of ≥1 mm ST segment depression on the ECG for ≥1 min.

In addition to the VEST, a two-channel ambulatory ECG (Holter) monitor (Space Labs) with leads V_1 and V_5 was placed on the chest for 22 patients to provide an independent measure of the ECG response. After proper placement of the VEST and Holter monitor were ensured, subjects were brought to the cardiovascular behavioral medicine laboratory.

Relaxation phase. In the laboratory, subjects were seated in a comfortable chair. They were then fitted with a blood pressure cuff attached to an automated vital signs monitor (Dynamap SX/P 1846) that provided blood pressure data. Patients were instructed to inform the experimenter of any symptoms during the study. They were then asked to sit quietly and relax for the baseline stabilization period. To facilitate relaxation, room lights were dimmed and patients wore headphones with taped sounds of a mountain stream or ocean waves.

Videotaped Structured Interview. Subjects underwent the Friedman Videotaped Structured Interview, which provides a measure of type A behavior and an index of behavioral reactivity (33). In accordance with the guidelines for this 20-

to 30-min standard interview format, subjects were asked a series of questions regarding time pressures, competitive orientation, events that provoke anger, and dealings with frustrating situations. The interview was administered in a manner that encouraged the subject to speak freely. As with any standard clinical interview, the interviewer was free to explore responses that were believed to contain further information on characteristics of interest (for example, anger, hostility and behavior reactivity pattern). The interview was videotaped and scored at a later time.

Mental stress testing. Patients performed mental arithmetic and choice reaction time tasks that have been used previously in the study of induced myocardial ischemia (19,21). The order of presentation of these tasks and the interview was randomized.

Mental arithmetic. Patients were instructed to mentally subtract serial 7s from an initial 4-digit number or add 2-digit numbers, or both, and provide the answers aloud. They were further instructed to perform this task as quickly and accurately as they could. Mistakes were corrected in a harsh tone, and reminders for quick performance were provided twice during the period, thereby ensuring that the task would be challenging to all patients.

Choice reaction time. Patients were instructed to watch a computer screen and follow the instructions provided. The first instruction, "REST," was displayed for 15 s. The next instruction, "GET READY," was displayed for 2 to 8 s (mean 5). The final instruction, "PRESS THE LETTER _" (a different letter was presented at each trial), was displayed for 1 s. After an appropriate key press response, the screen cleared for 5 s and the cycle was repeated for a total of 10 trials.

Exercise. After the 20-min postprotocol period, patients were asked to walk for 8 to 10 min on level ground at their normal pace. This was done to ascertain the effect of mild exercise on left ventricular function. After completion of this task, the VEST was removed and the patient was sent home with a questionnaire to complete.

Psychological assessment. The psychological profile was determined from responses during the Structured Interview and from the questionnaire battery.

Questionnaire. The take-home questionnaire battery comprised multiple standardized measures of hostility, anger and neuroticism. Hostility was measured by the Cook-Medley Hostility Scale (34), which contains 50 items answered on a true/false basis. Three factor scores indicative of cynicism, hostile affect and aggressive responding are derived from this scale. Anger as a stable personality trait, and mode of anger expression (expressed inwardly or suppressed [Anger-In], expressed outwardly [Anger-Out] or kept under control [Anger Control]) were assessed by the Spielberger Trait Anger Scale (35) and Spielberger Anger Expression Scale (36), respectively. On these scales, subjects indicate the degree to which they endorse statements descriptive of anger and anger expression, utilizing a 1 (not at all) to 4 (always) response. Neuroticism was assessed by the Spielberger Trait Anxiety Scale (37) and scales K, Hs, D and Hy on the Minnesota Multiphasic Personality Inventory (38,39).

Each of these scales has been applied previously in numerous studies (8,9,23,34,38,40,41), and their reliability, stability and validity in comparable patient groups have been established.

Structured Interview. Pattern and degree of behavioral reactivity were determined from the Structured Interview. Responses were scored for content (affirmative response to questions regarding walking and eating fast and being a hard-driving achiever), response style (voice modulation, volume and speed), psychomotor behaviors (vehement gestures accompanying responses, facial tics, fast and jerky movements and repetitive limb movements) and hostile or competitive attitudes (angry generalizations and distrust about the motives of others), as described previously (33). A total score ranging from 0 to 38 was derived, indicating an increasing presence of these behaviors. Despite the substantial degree of training required for administering and interpreting this protocol, it was selected over other methods because of its wider sampling of behavior (psychomotor manifestations and physiologic indicators), objective scoring criteria and continuous versus categoric score. All interview administration and scoring were performed by one investigator, with 25% of tapes also being scored in blinded fashion by another rater; both raters were trained to competence at the Meyer Friedman Institute. All ratings were made without knowledge of the left ventricular response to mental stress. Interobserver agreement on the presence and frequency of specific behaviors during the Structured Interview was 85%.

Statistical analysis. Data on left ventricular ejection fraction and relative volumes, heart rate and blood pressure were averaged within experimental conditions, with change from baseline scores calculated for each condition. Throughout, data are expressed as mean ± SD.

All statistical analyses were performed using the SAS Statistical Package for the Personal Computer. Univariate analysis with the Student *t* test was used as an initial strategy to individually determine the relationship between psychological variables and cardiovascular variables. In addition, a paired *t* test was used to determine the significance of changes in cardiovascular measures within groups. Multivariate analysis using ordinal logistic regression was then used to determine multivariate relationship among variables found significant with the *t* test. The logistic method fits a multiple regression model to a single binary-dependent variable, generating a chi-square statistic for the independent variables of interest, controlling for relationships among the independent variables. For our analyses, patient group served as the dependent variable. Behavioral reactivity/type A score from the Structured Interview, questionnaire scores for trait anger, aggressive responding, hostile affect and anger control, and change in exercise redistribution thallium-201 score served as independent variables, the latter in-

Table 1. Cardiovascular and Ventricular Indexes at Baseline and During Stress

Change From Baseline	Group I	Group II	p Value
Baseline			
HR (beats/min)	59.5 ± 8.6	66.5 ± 14.6	NS
SBP (mm Hg)	136.3 ± 30.4	118.9 ± 18.1	NS
DBP (mm Hg)	74.4 ± 11.1	71.3 ± 8.0	NS
Structured Interview			
HR (beats/min)	9.7 ± 9.4	8.6 ± 7.7	NS
SBP (mm Hg)	37.1 ± 18.4	37.9 ± 17.1	NS
DBP (mm Hg)	17.6 ± 10.6	19.7 ± 12.3	NS
ESV (%)	10.8 ± 5.7	4.0 ± 7.4	0.01
EDV (%)	2.7 ± 4.6	2.6 ± 4.9	NS
Mental arithmetic			
HR (beats/min)	7.3 ± 6.2	6.6 ± 6.7	NS
SBP (mm Hg)	29.7 ± 22.9	35.6 ± 15.7	NS
DBP (mm Hg)	13.6 ± 9.5	13.6 ± 7.6	NS
ESV (%)	15.8 ± 13.0	2.7 ± 5.8	0.008
EDV (%)	2.2 ± 2.5	1.1 ± 2.5	NS
Choice reaction time			
HR (beats/min)	3.8 ± 6.4	1.6 ± 5.2	NS
SBP (mm Hg)	17.1 ± 13.6	21.6 ± 13.2	NS
DBP (mm Hg)	4.4 ± 9.1	7.7 ± 6.7	NS
ESV (%)	−1.1 ± 2.7	−2.5 ± 5.6	NS
EDV (%)	−0.8 ± 3.9	0.3 ± 3.4	NS

Values are expressed as mean value ± SD. DBP = diastolic blood pressure; EDV = end-diastolic volume; ESV = end-systolic volume; Groups I and II indicate, respectively, patients with and without evidence of left ventricular dysfunction during mental arithmetic; HR = heart rate; SBP = systolic blood pressure.

cluded to control for disease severity across groups. A forward stepwise procedure with elimination and replacement was utilized, which allowed for the building of a best fit model for the dependent variable. For *t* tests, a $p < 0.01$ was used to determine significance; $p < 0.05$ was used for the logistic regression.

Results

Physiologic response to stress (Table 1). *Mental arithmetic.* Fifteen of 30 patients (Group I) had a decrease in left ventricular ejection fraction ≥0.05 (range 0.06 to 0.30) during mental arithmetic, with an average decrease of 0.14 ± 0.08 (Fig. 1). This compared with an average decrease of 0.003 ± 0.001 for the remaining 15 subjects (Group II). The initial effect was noted within the 1st 30 s of the mental arithmetic period, with the peak effect occurring within the 1st 2 min of the period; ejection fraction reverted to baseline values within 1 min into the subsequent rest period. These changes for Group I were accompanied by an average increase in relative end-diastolic volume of 2.2 ± 2.5% (p = NS) and an average increase in relative end-systolic volume of 15.8 ± 13.0% ($p < 0.008$). The average cumulative duration of the ≥0.05 decrease for Group I was 3.8 ± 2.1 min, or 78% of the 5-min stress period. During this time,

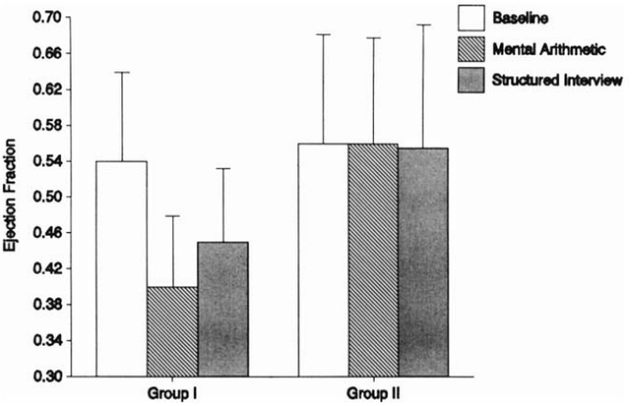

Figure 1. Left ventricular ejection fraction (mean ± SD) during initial baseline measurement, Videotaped Structured Interview and mental arithmetic in Group I and Group II patients. The decrease in ejection fraction from baseline tasks in Group I patients is significant ($p < 0.001$).

no changes were noted on the ECG, either by Holter monitor or the VEST system. Furthermore, no patient reported any symptoms of angina during this or any other part of the study.

At baseline, Groups I and II were comparable with respect to heart rate, systolic blood pressure and diastolic blood pressure. Both groups demonstrated significant and comparable increases from baseline ($p < 0.0001$ for all) in heart rate, systolic blood pressure and diastolic blood pressure during mental arithmetic (Table 1).

Videotaped Structured Interview. The Structured Interview was also found to provoke an asymptomatic decrease in left ventricular ejection fraction for approximately half of the study group. During this task, the 15 subjects in Group I plus an additional 3 subjects from Group II (total 18) had such a decrease (range 0.06 to 0.25; mean decrease 0.09 ± 0.04) (Fig. 1). As with mental arithmetic, the initial effect was noted within 30 s of task initiation, with the peak effect occurring within 2 min. Ejection fraction reverted to baseline within 1 min of the subsequent rest period in all but one case. The average cumulative time of ejection fraction decrease ≥0.05 was 13.7 ± 9.1 min or 56 ± 37% of the total interview period. Decreases in ejection fraction were accompanied by an average increase in relative end-diastolic volume of 2.7 ± 4.6% (p = NS) and end-systolic volume of 10.8 ± 5.7% ($p < 0.01$). During the interview, significant increases from baseline ($p < 0.0001$ for all) were noted in heart rate, systolic blood pressure and diastolic blood pressure; these increases were comparable to those found during mental arithmetic. There were no differences in these variables between subjects with and without an abnormal ventricular response (Table 1).

Choice reaction time. No significant changes were noted in ejection fraction during this task for any patient. Minimal nonsignificant changes were seen in heart rate, systolic

Table 2. Patient Characteristics

	Group I	Group II
Age (yr)	66 ± 7	62 ± 10
Beta-blockers	5	4
Calcium channel antagonists	8	7
Hypertension	9	6
Diabetes mellitus	1	1
Prior infarction	8	8
Prior revascularization	4	5
Basal LVEF (%)	54 ± 10	56 ± 12

Values are expressed as mean value ± SD or number of patients. p = NS for all variables. LVEF = left ventricular ejection fraction; other definitions as in Table 1.

blood pressure and diastolic blood pressure, with no significant group differences emerging (Table 1).

Walking exercise. Groups I and II had comparable increases in ejection fraction (0.09 vs. 0.12, p = NS), heart rate (21 vs. 26, beats/min, p = NS) and end-diastolic volume (9.1 vs. 8.6%, p = NS), and a comparable decrease in end systolic volume (−5.8 vs. −6.8%, p = NS) during this mild exercise. Although no group differences were found, these measures were significantly elevated compared with baseline values ($p < 0.0007$ for all). Blood pressure was not monitored during this task.

Clinical characteristics. Patients in Groups I and II were also compared with respect to variables of clinical interest (Table 2). No group differences were noted for age, baseline left ventricular ejection fraction or concomitant clinical conditions (hypertension, diabetes mellitus, prior myocardial infarction or prior revascularization). In addition, no group differences were noted with regard to antianginal medication regimen (beta-blockade, calcium antagonists or long-acting nitrates).

In an effort to determine whether Groups I and II were comparable with respect to severity of coronary artery disease, exercise stress thallium-201 test results were examined. No group differences were found for test duration, baseline and peak heart rate, systolic blood pressure, diastolic blood pressure or maximal rate-pressure product at the time of ischemia. In addition, thallium-201 defect scores at baseline and redistribution were comparable, as was heart/lung thallium-201 uptake ratio (Table 3). Neither maximal stress test radionuclide ventriculography nor angiographic assessment was routinely performed in the study cohort.

Psychological profile (Table 4). ***Behavioral reactivity pattern/type A.*** Scores on the Structured Interview were significantly different for Groups I and II (17.9 ± 4.7 vs. 10.9 ± 4.9, respectively, $p < 0.003$). These data indicate a greater number and frequency of behavioral reactivity indicators during the Structured Interview for Group I compared with Group II patients and, hence, a higher score for type A behavior.

To determine whether a quantitative relationship existed between the frequency of behaviors observed during the Structured Interview (hence, type A behavior pattern score) and the percent of the Structured Interview task period with evidence of left ventricular dysfunction, Pearson correlation analysis was conducted between these variables for patients with evidence of left ventricular dysfunction during this task. A strong significant relationship ($r = 0.70$, $p < 0.002$) was found between this measure of behavioral reactivity and the duration of left ventricular dysfunction during this task.

Table 3. Exercise Quantitative Stress Thallium-201 Imaging

	Group I	Group II
Test duration (min)	10.1 ± 2.3	10.1 ± 2.6
Baseline		
HR (beats/min)	73.8 ± 15.2	68.7 ± 10.0
SBP (mm Hg)	141.8 ± 28.8	130.6 ± 21.3
DBP (mm Hg)	77.1 ± 6.8	76.6 ± 13.1
Peak		
HR (beats/min)	138.7 ± 25.6	129.7 ± 19.7
SBP (mm Hg)	167.9 ± 23.2	172.1 ± 29.1
DBP (mm Hg)	79.3 ± 10.5	80.4 ± 11.8
Peak rate-pressure product	23,307 ± 5,569	22,485 ± 5,754
Exercise thallium-201 score		
Baseline	7.7 ± 6.8	7.8 ± 8.9
Redistribution	3.7 ± 3.7	4.1 ± 7.5
Change	4.0 ± 3.7	3.7 ± 3.3
Heart/lung ratio	0.39 ± 0.07	0.38 ± 0.08

p = NS for all variables. Definitions and abbreviations as in Table 1.

Hostility. Scores on the three factors of the Hostility Scale were examined independently. For the aggressive responding factor and the hostile affect factor, significant differences were noted, with Group I patients scoring higher ($p < 0.001$ and $p < 0.003$, respectively). No group differences were noted for the cynicism factor. These data indicate an admission of anger and impatience in social settings

Table 4. Psychological Factors for Group I Compared With Group II

	Group I	Group II	p Value
Behavioral Reactivity Pattern	17.9 ± 4.7	10.9 ± 4.9	0.003
Hostile Affect	3.6 ± 0.8	2.1 ± 1.0	0.003
Aggressive Responding	5.9 ± 0.8	4.1 ± 1.3	0.001
Trait Anger	24.2 ± 4.2	16.9 ± 2.3	0.0001
Anger Control	7.9 ± 1.4	10.6 ± 1.2	0.0001
Anger-In	17.3 ± 4.4	14.7 ± 3.8	NS
Anger-Out	14.9 ± 3.4	14.8 ± 3.8	NS
Cynicism	7.9 ± 3.3	6.6 ± 3.0	NS
Trait Anxiety	21.5 ± 6.9	17.4 ± 5.8	NS
MMPI scale			
Hs (K corrected)	23.8 ± 8.2	27.3 ± 5.4	NS
D	29.5 ± 7.2	27.4 ± 6.1	NS
Hy	24.2 ± 6.6	26.3 ± 5.7	NS

MMPI = Minnesota Multiphasic Personality Inventory.

and a greater tendency to use anger as an instrumental response to potential frustrations.

Anger. For trait anger, significant group differences were revealed ($p < 0.0001$), with Group I scoring higher. For anger control, significant group differences were also found ($p < 0.0001$), with Group I scoring lower. These data indicate more frequent experience of anger, more easily aroused anger and a lesser likelihood of controlling anger for Group I compared with Group II. No group differences were noted for Anger-In or Anger-Out. Thus, the experience of anger, irrespective of whether expressed inwardly or outwardly, was characteristic of Group I patients.

Neuroticism. The K scale–corrected scores on the Hs, D and Hy scales of the Minnesota Multiphasic Personality Inventory were analyzed individually, with no group differences emerging. Group differences were also not found on the Spielberger Anxiety Scale. These findings are consistent and show no group differences for measures of neuroticism, anxiety, depression or somatization.

Multivariate analysis. Those independent variables that had demonstrated univariate group differences were included in an ordinal logistic regression with patient group as the dependent variable. The specific independent variables tested were behavioral reactivity/type A score from the Structured Interview and questionnaire scores for trait anger, aggressive responding, hostile affect and anger control; change in exercise redistribution thallium-201 score (redistribution score minus score at rest) was included to control for disease severity. Of these variables, aggressive responding (chi-square 12.50, $p < 0.0004$), trait anger (chi-square 9.66, $p < 0.0019$) and type A (chi-square 6.17, $p < 0.014$) remained significant, accounting for most of the variance (the residual chi-square value was not significant).

Discussion

Psychological factors. A subset of psychological factors were associated with the silent expression of left ventricular dysfunction in our sample of 30 patients with stable coronary artery disease. In comparison with their clinically similar cohort, the 15 patients with stress-related ventricular dysfunction during mental arithmetic scored higher on measures of hostile affect, aggressive responding, trait anger and behavioral reactivity/type A and scored lower on a measure of anger control. Several other psychological factors, including anxiety and neuroticism, did not distinguish the two groups of patients. Furthermore, both groups had a similar magnitude of change in heart rate and systolic/diastolic blood pressure in response to this mental stress. Baseline left ventricular function, extent of reversible perfusion abnormalities on thallium-201 imaging, the use and nature of antianginal medication and several clinical and historic variables were also similar in the two groups.

Multivariate analysis showed that measures of aggressive responding, trait anger and behavioral reactivity/type A contributed unique variance to mental stress-provoked silent ventricular dysfunction. These findings describe a person who is emotionally challenged by and experiences anger during routine daily events. Although such a person is further likely to express the anger aggressively and endorse aggressive behavior as appropriate for routine social interactions, it is the ease with which these individuals become emotionally aroused and the presence of anger as a natural constituent of this arousal that are highlighted. These findings are consistent with a growing body of research suggesting a role for anger/hostility as a risk factor for coronary artery disease (8–13) and highlighting the potential ischemic impact of an angry response style in the setting of this disease (42).

Structural Interview. With respect to left ventricular ejection fraction, the response to the Structured Interview was similar, albeit slightly less in magnitude, to that found with the more commonly used method of mental arithmetic for provoking mental stress and secondary ventricular dysfunction. Furthermore, the strong correlation found between the Structured Interview score and the duration of left ventricular dysfunction during the Structured Interview demonstrates the potentially deleterious nature of type A behavior for patients with coronary artery disease. This finding is clinically important, given the methods used for the Structured Interview. The Structured Interview is interactive and designed, in a manner analogous to natural social interaction, to elicit the typical behavioral response style of the individual when he or she encounters even mildly provocative or stressful conditions (33). In addition, it enables the interviewer to assess the presence of the target response style (for example, hostile, angry or hurried) and whether this response style is accompanied by behavioral/emotional arousability (7): a higher score on the Structured Interview indicates a greater frequency of the behaviors that comprise the type A pattern and greater emotional arousal in conjunction with these behaviors. In addition, because of the analogue nature of the Structured Interview, higher scores indicate an increased likelihood of the target behaviors and emotional arousal occurring routinely in a wide range of settings. Hence, patients with coronary artery disease who show the behaviors and emotional arousal measured by the Structured Interview may be at risk for frequent silent myocardial ischemia throughout their day, and treatments directed toward the alteration of this class of behaviors (33) may be a useful adjunct in the treatment of (silent) ischemia.

Possible mechanisms. The absence of ST segment changes or symptoms of angina pectoris during episodes of left ventricular dysfunction was consistent with the findings of several prior studies. Kayden et al. (31) found that during left anterior descending coronary angioplasty, balloon inflation was accompanied by a prompt decrease in left ventricular ejection fraction in 17 of 18 patients. This decrease, however, was accompanied by chest pain in only 10 patients and ST segment changes in only 7 patients. Deanfield et al.

(20) studied changes in myocardial perfusion during mental stress and physical exercise in 16 patients with chronic stable angina, using serial myocardial imaging with rubidium-82 positron emission tomography. Mental stress provoked perfusion abnormalities in 12 of these patients, with ST segment changes and anginal symptoms occurring in only 8 and 5 patients, respectively. In contrast, exercise provoked perfusion abnormalities and ST segment changes in all patients and anginal symptoms in 15. Recently, Giubbini et al. (43) found reversible perfusion abnormalities during mental stress in 20 of 24 patients with exercise-induced myocardial ischemia. The mental stress–provoked abnormalities were not associated with either ST segment changes or anginal symptoms in any patient and were essentially seen in the same segments that showed perfusion abnormalities during exercise. Similarly, Ironson et al. (42) found no ST segment changes during an anger recall–provoked decrease in left ventricular ejection fraction, despite finding ST segment depression during exercise stress among this same set of patients. Rozanski et al. (18) performed serial gated radionuclide angiography during several types of mental stress in 39 patients with coronary artery disease. Mental stress provoked segmental wall motion abnormalities in 59% of patients and a decrease in left ventricular ejection fraction in 36%. The wall motion abnormalities were observed in the same segments that had previously shown reversible perfusion abnormalities on stress thallium imaging. Moreover, these mental stress–induced wall motion abnormalities were accompanied by ST segment changes or anginal symptoms, or both, in <25% of the patients tested.

These data indicate that mental stress can result in clinically significant myocardial wall motion abnormalities, perfusion abnormalities and a decrease in global left ventricular ejection fraction in a substantial proportion of patients with coronary artery disease. In contrast to exercise-provoked ischemia, mental stress–provoked ischemia appears to be unaccompanied by ST segment changes or anginal symptoms; hence, it is more likely to be silent. Traditional clinical and ECG markers may therefore be insufficient for evaluating mental stress–related myocardial ischemia. Hence, the use of more sensitive tools such as those used in this study may be important when examining this phenomenon.

Changes in loading conditions can result in significant changes in ejection fraction, independent of any alteration in myocardial perfusion. It is therefore possible that the significant increases in systolic and diastolic blood pressure observed during mental stress and the Structured Interview may have been responsible for the decrease in ejection fraction in Group I patients. Although this possibility cannot be fully excluded, it is important to note that the magnitude of the increases in blood pressure and heart rate were comparable for both Group I and Group II patients. Therefore, we believe the decrease in ejection fraction during mental stress and the Structured Interview was real and indicative of underlying ischemia.

The absence of group differences in markers of myocardial oxygen demand (heart rate and systolic blood pressure) suggest that a change in oxygen supply may underlie mental stress–provoked silent myocardial ischemia. This hypothesis is consistent with what is known about the physiologic response pattern of persons whose psychological profile is similar to that seen in our Group I patients. These individuals show significantly higher daytime urinary levels (44,45) and significant increases in mental stress–induced circulating levels of epinephrine, norepinephrine and cortisol (45,46). These compounds have documented supply side effects (47–48), and circulating levels have been found to correlate with the frequency of silent ischemia during up to 72-h Holter monitoring periods (49). In addition, these individuals have shown alterations in the ratio of peripheral alpha$_2$- to beta$_2$-receptor density, consistent with alpha-receptor–mediated coronary artery vasoconstriction (50).

Further support for the supply hypothesis is found in a recent demonstration of mental stress–induced coronary artery vasospasm during cardiac catheterization in patients with coronary artery disease (51). In that study, however, acetylcholine was also found to produce paradoxic vasoconstriction at the point of coronary artery stenosis, indicating endothelial dysfunction and implicating endothelial factors in the mental stress/ischemia equation. Hence, although a reduction in myocardial oxygen supply appears to be the likely culprit in mental stress–induced (silent) myocardial ischemia, the mechanisms of action—whether related to catecholaminergic effects on platelets and vasomotor tone (47,48) or to endothelial substances and dysfunction—and the site of action—whether proximal or distal—require further examination.

Limitations of the study. Although the results of this study are provocative, there are several additional points to consider. The study was undertaken with a relatively select group of patients with coronary artery disease, characterized by older age, male gender and veteran status. Furthermore, each patient had demonstrated active ischemia on stress thallium-201 testing. Hence, the generalizability of these results to other patients with coronary artery disease cannot be assumed. In addition, the VEST apparatus did not allow for the measurement of segmental changes in left ventricular function, but only for the measurement of global change. Finally, although silent ventricular dysfunction was provoked by mental stress and the Structured Interview, the prognostic significance of this dysfunction was not evaluated. The prognostic significance of VEST-measured left ventricular dysfunction has been addressed previously. Kayden et al. (31) used the VEST to monitor ventricular function during routine activity in a group of 33 patients after thrombolytic therapy. Adverse cardiac events occurred in 8 of 12 patients with demonstrated ventricular dysfunction on VEST monitoring, but in only 3 of 21 patients showing no

such dysfunction. A similar evaluation of patients showing mental stress–induced ventricular dysfunction awaits future consideration.

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