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Effects of Mental Stress on Left Ventricular and Peripheral Vascular Performance in Patients With Coronary Artery Disease

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Objectives. **We sought to investigate the mechanism of a mental stress–induced fall in left ventricular ejection fraction (LVEF) in patients with coronary artery disease.**

Background. **Mental stress induces a fall in LVEF in a significant proportion of patients with coronary artery disease. This is accompanied by an increase in heart rate, blood pressure and rate–pressure product. Whether the mental stress–induced fall in LVEF is due to myocardial ischemia, altered loading conditions or a combination of both is not clear.**

Methods. **Left ventricular (LV) function was studied noninvasively by serial equilibrium radionuclide angiocardiography and simultaneous measurement of peak power, a relatively afterload-independent index of LV contractility, in 21 patients with coronary artery disease (17 men, 4 women) and 9 normal subjects (6 men, 3 women) at baseline, during mental stress and during exercise. Peripheral vascular resistance (PVR), cardiac output (CO), arterial and end-systolic ventricular elastance (E_a, E_{es}) and ventriculoarterial coupling (V/AC) were also calculated. Patients underwent two types of mental stress—mental arithmetic and anger recall—as well as symptom-limited semisupine bicycle exercise.**

Results. **Nine patients (43%) had an absolute fall in LVEF of ≥5% (Group I) in response to at least one of the mental stressors, whereas the remaining patients did not (Group II). Group I and Group II patients were similar in terms of baseline characteristics. Both groups showed a significant but comparable increase in systolic blood pressure (15 ± 7 vs. 9 ± 10 mm Hg, p = 0.12) and a slight increase in heart rate (7 ± 4 vs. 8 ± 7 beats/min, p = 0.6) and a comparable increase in rate–presure product (2.2 ± 0.9 vs. 1.9 ± 1.2 beats/min × mm Hg, p = 0.6) with mental stress. However, PVR increased in Group I and decreased in Group II (252 ± 205 vs. −42 ± 230 dynes·s·cm^{-5}, p = 0.006), and CO decreased in Group I and increased in Group II (−0.2 ± 0.4 vs. 0.6 ± 0.7 liters/min, p = 0.02) with mental stress. There was no difference in the change in peak power (p = 0.4) with mental stress. With exercise, an increase in systolic blood pressure, heart rate, rate–pressure product and CO and a fall in PVR were similar in both groups. Of the two mental stressors, anger recall resulted in a greater fall in LVEF and a greater increase in diastolic blood pressure. Exercise resulted in a fall in LVEF in 7 patients (33%). However, exercise-induced changes in LVEF and hemodynamic variables were not predictive of mental stress–induced changes in LVEF and hemodynamic variables.**

Conclusions. **Abnormal PVR and E_a responses to mental stress and exercise are observed in patients with a mental stress–induced fall in LVEF. Peripheral vasoconstrictive responses to mental stress contribute significantly toward a mental stress–induced fall in LVEF.**

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A number of studies have examined specific cardiovascular effects of mental stress in patients with coronary artery disease (1–6). Most of these studies have focused on left ventricular ejection fraction (LVEF). In selected patients with coronary artery disease, a significant fall in LVEF has been observed during mental stress, generally accompanied by a modest increase in heart rate and a greater increase in blood pressure and derived rate–pressure product (1,4). Two recent studies have demonstrated a negative prognostic significance of either a mental stress–induced fall in LVEF or transient wall motion abnormalities. Nearly three times as many adverse cardiac events occurred during follow-up in patients with mental stress–induced left ventricular (LV) dysfunction (7,8). The relative contributions of mental stress–related alterations in loading conditions and mental stress–induced altered myocardial contractility secondary to ischemia in mediating this fall in LVEF are not fully known. The purpose of this study was to further investigate the mechanism(s) of a mental stress–induced fall in LVEF by assessing load-independent indexes of LV function as well as peripheral vascular indexes derived from a combination of noninvasive techniques. Studies were obtained during mental stress and semisupine bicycle exercise in patients with coronary artery disease, as well as in a group of control subjects.

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Abbreviations and Acronyms

CO = cardiac output
E_a = arterial elastance
E_{es} = end-systolic ventricular elastance
EDV = end-diastolic volume
ESV = end-systolic volume
LV = left ventricular
LVEF = left ventricular ejection fraction
PVR = peripheral vascular resistance
SV = stroke volume
V/AC = ventriculoarterial coupling

Methods

Patients. Twenty-one patients with chronic coronary artery disease (17 men, 4 women; age 56 ± 11 years) were studied. Ten patients had a history of hypertension, 13 had a history of angina and 16 had a previous myocardial infarction. Five patients had undergone coronary artery bypass graft surgery and eight had undergone percutaneous transluminal coronary angioplasty ≥6 months before the study. Fifteen patients had reversible or partially reversible perfusion abnormalities on recent stress perfusion imaging. Five patients had fixed defects on previous perfusion images. The one patient who did not undergo perfusion imaging had single-vessel coronary artery disease demonstrated by coronary angiography. Six patients were receiving beta-blockers, 16 calcium channel blockers, 5 nitrates and 3 angiotensin-converting enzymes inhibitors. All patients continued their medication during the study. Patients with overt congestive heart failure, unstable angina, myocardial infarction or a myocardial revascularization procedure within the last 6 months and those in atrial fibrillation were excluded. Patients who were unable to perform semisupine bicycle exercise were excluded. The baseline LVEF for the patients was 55 ± 10%. A group of nine normal healthy subjects with a low likelihood (<3%) of coronary artery disease was also studied (6 men, 3 women; age 38 ± 11 years). These subjects were entirely asymptomatic and had no risk factors for coronary artery disease and were not taking any medications. Their baseline LVEF was 61 ± 8%. The study was approved by the Institutional Human Investigation Committee.

Protocol. Serial equilibrium radionuclide angiocardiography was performed for the determination of count-based LV volumes (9), LVEF and cardiac output (CO). A Doppler-based forearm pressure measuring device was used for the simultaneous measurement of central arterial pressure and waveform (10,11). A combination of the volumetric and central arterial pressure and waveform data was used for the calculation of LV peak power, a relatively afterload-independent LV contractility index (10,11). Peripheral vascular resistance (PVR), stroke work, end-systolic ventricular elastance (E_{es}), arterial elastance (E_a) and ventriculoarterial coupling (VA/C) ratios were also derived, as described later, to determine changes in LV contractility and afterload and the relation between afterload and ventricular contractility (12–15).

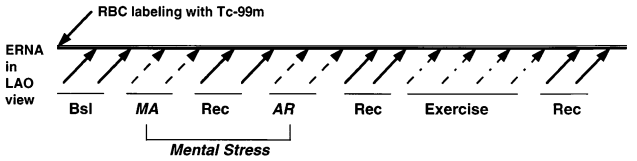

Figure 1. Study protocol. AR = anger recall; Bsl = baseline; ERNA = equilibrium radionuclide angiocardiography; LAO = left anterior oblique; MA = mental arithmetic; RBC = red blood cell; Rec = recovery; Tc-99m = technetium-99m.

All studies were carried out in the morning. Patients were allowed to have a light breakfast at least 2 h before the study. After obtaining written, informed consent, red blood cells were labeled with 20 to 25 mCi of technetium-99m using the standard labeling technique (16). After blood pool labeling, patients were positioned on a semisupine bicycle and the gamma camera was positioned in the left anterior oblique view. The blood pressure cuff and Doppler arterial probe of the Cardiospec 2000 device were positioned on the right forearm as previously described (10). After proper positioning, serial radionuclide angiograms were acquired in the left anterior oblique view. Each view was acquired for 3 min. Two acquisitions were made at baseline for 3 min each. This was followed by two different mental stress tasks for 6 min each, separated by an interval of 6 min to allow for recovery to baseline. Recovery between the two tasks was judged by the return of heart rate and blood pressure to baseline. Two separate radionuclide acquisitions were made during each stressor. Mental stress was followed by a recovery period of 6 to 7 min and then symptom-limited bicycle ergometry with continuous 12-lead electrocardiographic monitoring. Exercise was started at an initial work load of 25 W/min. The work load was increased by 25 W in 3-min stages. Exercise was limited by symptoms of chest pain, fatigue, shortness of breath, achievement of maximal age-adjusted heart rate, ≥2 mm ST segment depression or hypotension. Exercise was followed by a recovery period of 6 min. Equilibrium radionuclide angiocardiograms were obtained every 3 min during the entire study. Central arterial blood pressure and arterial pressure curves were obtained noninvasively using the Cardiospec 2000 device every 1 to 2 min from the forearm Doppler sensor during the entire study. Figure 1 describes the study protocol.

Mental stress. Two different mental stressors—mental arithmetic and anger recall—were given in that order for 6 min each, separated by a rest/recovery period of 6 min. For mental arithmetic, subjects were given a 3-digit number and were asked to subtract 7 sequentially from this number. They were asked to do this rapidly and accurately. Any mistakes were corrected harshly. For anger recall, patients were asked to recollect a recent annoying and/or frustrating event. This event was discussed in further detail with the patient, with the insertion of frequent irritative and annoying questions relating to the event.

Radionuclide angiocardiographic and volume measurements. A standard gamma camera with a general all-purpose collimator interfaced with a minicomputer was used for equi-

librium radionuclide angiocardiography. Data were acquired at a cycle of 16 frames/RR interval. LV time–activity curves were generated with four Fourier harmonics, using a semiautomated program (17). LVEF was calculated from serial time–activity curves. Absolute LV volumes were obtained using the method of Massardo et al. (9). In brief, the LV end-diastolic volume was derived from a ratio of total counts in the end-diastolic region of interest to a reference pixel (of known dimension) with maximal counts. This method has been incorporated into our automated software for equilibrium radionuclide angiocardiography analysis. The absolute peak ejection flow rate was calculated from the first derivative of the first half of the LV volume curve (10). Regional wall motion was assessed visually in all equilibrium studies to detect the appearance of new wall motion abnormalities or worsening of the existing wall motion abnormalities during mental stress or exercise.

Noninvasive central arterial pressure measurement. A prototype noninvasive device (Cardiospec 2000) was used to measure central arterial pressure. The theoretic principle of this technique has been described previously (11,18). In brief, a combination of a 5-MHz Doppler flow probe placed over the brachial artery, a standard sphygmomanometric cuff with a microprocessor-controlled deflation device and a standard ECG monitoring system was used for obtaining a composite cardiac systolic pressure curve from an average of 30 to 40 cardiac cycles. To achieve this, the pressure in the cuff was raised above the systolic pressure (Doppler senses no flow). As the cuff is deflated, the Doppler signal reappears and the time delay from the preceding R wave of the ECG to the onset of brachial flow is measured. This time delay is plotted as a function of cuff pressure. The resulting curve is equivalent to the upstroke of the central arterial pressure wave. An excellent correlation ($r = 0.99$) has been observed between simultaneously measured noninvasive and invasive pressure in the ascending aorta (11).

Left ventricular peak power. Cardiac power is defined as the amount of work per unit time and is calculated by multiplying flow by instantaneous pressure: cardiac power = pressure × dv/dt, where dv/dt is the rate of change of flow (the first derivative of the LV volume curve), thus representing the systolic flow, and the pressure is the corresponding systolic aortic blood pressure. Cardiac power corresponding to the maximal flow rate (dv/dt_{max}), normalized to the end-diastolic volume (EDV), is the peak power. Peak power is an early ejection phase index of LV contractility and is relatively afterload independent (10,15). The LV power curve was obtained by multiplying each point of pressure curve by its corresponding point on the dv/dt curve. This was done off-line after aligning the LV volume curve with the corresponding aortic pressure curve. A single LV volume curve was obtained from each equilibrium radionuclide angiocardiographic study, and one or two aortic pressure curves were obtained for each volume curve. Plotting of the power curve and calculation of peak power was done automatically using the software installed on the Cardiospec 2000 computer.

Hemodynamic variables. The following hemodynamic variables were derived: 1) Mean arterial blood pressure (P_m) = (systolic blood pressure + 2× diastolic blood pressure)/3. 2) Stroke volume (SV) was calculated from EDV and LVEF (SV = EDV × LVEF%). 3) EDV and LVEF were obtained from the equilibrium radionuclide angiocardiogram as described previously. 4) End-systolic volume (ESV) was derived from EDV and stroke volume (ESV = EDV − SV). 5) CO was derived from SV and heart rate (CO = heart rate × SV). 6) PVR was calculated from P_m and CO (PVR = 80 × [P_m − 5]/CO) in dynes·s·cm^{-5}. 7) The rate–pressure product was calculated as heart rate × systolic blood pressure. 8) End-systolic pressure (P_{es}) was calculated as (systolic blood pressure × 2 + diastolic blood pressure)/3. 9) Stroke work was calculated as P_{es} × SV. 10) E_a, a more comprehensive index of vascular load, incorporating both pulsatile and nonpulsatile elements of arterial load, was calculated as P_{es}/SV (14,19). 11) E_{es} was calculated as ([E_a × SV]/ESV = P_{es}/ESV]) (14,19). 12) V/AC, an index of the efficiency of transfer of hydraulic power from the ventricle to the arterial system (a ratio of 1 results in maximal efficiency), was derived as E_a/E_{es} = ESV/SV (20).

Statistical analysis. The patient group was compared with the group of normal subjects. The patient group was also divided into two subgroups based on the abnormal LVEF response to mental stressors. As in previous studies from our laboratory, patients with a fall of ≥5% in LVEF with at least one mental stressor were considered as mental stress positive (Group I), and the remaining mental stress–negative patients were considered as Group II (1,7). After this dichotomization, the data from both mental stressors were averaged for each patient to obtain a single value for mental stress. For exercise, the peak exercise value was chosen. The data are presented as the mean value ± SD. Unpaired *t* tests were used for continuous variables, and the chi-square test was used for discrete variables to compare the two groups of patients with each other and with normal subjects. Paired *t* tests were used to compare the paired data. A value <0.05 was considered significant.

The data were also analyzed using repeated measures analysis of variance (PROC GLM in SAS) to compare different variables before and after the interventions (mental stress and exercise) to detect the interaction between various groups and types of intervention. The results of the two analyses were not different. For the sake of clarity of presentation, only the results using chi-square and *t* tests are shown.

Results

Baseline data. Table 1 shows the baseline hemodynamic data of the patients and the normal subjects. The rest LVEF and heart rate were not significantly different between the two groups. The patients had higher systolic and diastolic blood pressures and lower SV and CO compared with the normal subjects. The rest rate–pressure product, PVR, peak power, stroke work and E_{es} were not different. However, patients had higher E_a compared with normal subjects.

Table 1. Baseline Hemodynamic Characteristics of Patients and Normal Subjects

Variable	Patients (n = 21)	Normal Subjects (n = 9)	p Value
LVEF (%)	55 ± 10	61 ± 8	0.16
SV (ml)	83 ± 24	105 ± 27	0.05
HR (beats/min)	70 ± 15	69 ± 10	0.9
SBP (mm Hg)	154 ± 22	136 ± 12	0.005
DBP (mm Hg)	86 ± 11	75 ± 9.0	0.011
CO (liters/min)	5.7 ± 1.4	7.4 ± 2.0	0.04
RPP (10^3, mm Hg/min)	10.7 ± 2.6	9.5 ± 0.9	0.06
PVR (dynes·s·cm^{-5})	1,529 ± 318	1,202 ± 463	0.08
PP (W/ml)	4.3 ± 1.3	4.4 ± 0.8	0.8
SW (10^3, mm Hg/ml)	11.2 ± 4.6	12.0 ± 2.7	0.5
E_a (mm Hg/ml)	1.6 ± 0.3	1.2 ± .03	0.003
E_{es} (mm Hg/ml)	2.2 ± 0.9	2.1 ± 1.7	0.9
V/AC	0.9 ± 0.4	0.7 ± 0.3	0.13

Data presented are mean value ± SD. CO = cardiac output; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; E_a = arterial elastance; E_{es} = end-systolic ventricular elastance; HR = heart rate; PP = (left ventricular) peak power; PVR = peripheral vascular resistance; RPP = rate–pressure product; SBP = systolic blood pressure; SW = stroke work; SV = stroke volume; V/AC = ventriculoarterial coupling.

Changes in hemodynamic data with mental stress. In patients with coronary artery disease, mental stress resulted in a small increase in heart rate (8 ± 6 beats/min), a slight reduction in SV (−5 ± 8 ml), an increase in systolic (12 ± 9 mm Hg) and diastolic (5 ± 9 mm Hg) blood pressure, a commensurate increase in rate–pressure product, a minimal increase in CO (0.3 ± 0.7 liters/min), a minimal increase in PVR (84 ± 261 dynes·s·cm^{-5}), a small increase in peak power (0.3 ± 0.6 W/ml) and a minimal increases in stroke work, E_a, E_{es} and V/AC. When comparing mental stress–induced hemodynamic changes between patients with coronary artery disease and normal subjects, no differences were observed in LVEF, SV, heart rate, systolic and diastolic blood pressure and rate–pressure product (Table 2). However, PVR increased in patients with coronary artery disease, whereas it decreased in normal subjects ($p = 0.01$). There was less increase in CO ($p = 0.01$) and less increase in stroke work ($p = 0.02$) in patients with coronary artery disease compared with normal subjects (Table 2). There was a trend toward a greater increase in E_a in patients compared with normal subjects ($p = 0.057$). There was no difference in changes in peak power, E_{es} and V/AC.

Nine patients (43%) (Group I) developed a fall of ≥5% in LVEF with at least one mental stress task (two with both tests, three with mental arithmetic alone and four with anger recall alone). There was no correlation between the reversibility on previous myocardial perfusion images and a mental stress–induced fall in LVEF (6 [75%] of 8 patients in Group I and 9 [75%] of 12 patients in Group II had a reversible perfusion abnormality). Table 3 describes the hemodynamic changes with mental stress and exercise in Group I patients compared with the remaining 12 Group II patients (57%) who had no fall or <5% fall in LVEF with mental stress. The data for both mental stressors were averaged for each group after the initial dichotomization, based on an abnormal LVEF response to at least one mental stressor. None of the patients in either group had any ECG changes of ischemia with mental stress, although two patients had angina with mental stress (both in Group I with anger recall). New regional wall motion abnormalities were observed during mental stress in seven patients (three with both stressors, one with mental arithmetic alone and three with anger recall alone). Of the normal subjects, three had a fall in LVEF (all with anger recall), but none had regional wall motion abnormalities, chest pain or ST segment depression with mental stress.

Table 2. Comparison of Changes in Various Hemodynamic Variables With Mental Stress and Exercise in Patients With Coronary Artery Disease and Normal Subjects and Between Mental Stress and Exercise in Each Group

	Mental Stress			Exercise			Mental Stress Versus Exercise (p value)	
Variable	Patients (n = 21)	Normal Subjects (n = 9)	p Value	Patients (n = 21)	Normal Subjects (n = 9)	p Value	Patients	Normal Subjects
LVEF (%)	−2 ± 3	0 ± 3	0.15	0 ± 10	14 ± 11	0.002	0.15	0.009
SV (ml)	−5 ± 8	3 ± 12	0.1	1 ± 17	28 ± 33	0.006	0.1	0.05
HR (beats/min)	8 ± 6	11 ± 8	0.20	47 ± 28	70 ± 26	0.03	< 0.001	< 0.001
SBP (mm Hg)	12 ± 9	12 ± 5	0.8	23 ± 23	59 ± 15	< 0.001	0.06	< 0.001
DBP (mm Hg)	5 ± 9	10 ± 5	0.2	5 ± 14	5 ± 9	0.09	0.9	0.14
CO (liters/min)	0.3 ± 0.7	1.2 ± 0.9	0.01	3.9 ± 3.1	10.6 ± 5.5	< 0.001	<0.001	0.001
RPP (10^3, mm Hg/min)	2.0 ± 1.0	2.3 ± 1.4	0.9	10.7 ± 6.9	17.9 ± 6.1	0.011	< 0.001	< 0.001
PVR (dynes·s·cm^{-5})	84 ± 261	−53 ± 149	0.01	−547 ± 521	−735 ± 400	0.3	< 0.001	0.001
PP (W/ml)	0.3 ± 0.6	0.4 ± 0.8	0.6	2.2 ± 2.3	7.2 ± 2.9	< 0.001	0.001	< 0.001
SW (10^3, mm Hg/ml)	0.12 ± 0.97	1.50 ± 1.37	0.02	1.61 ± 2.62	8.42 ± 5.66	< 0.001	0.2	0.007
E_a (mm Hg/ml)	0.25 ± 0.28	0.05 ± 0.18	0.057	0.19 ± 0.46	0.1 ± 0.34	0.6	0.54	0.6
E_{es} (mm Hg/ml)	0.13 ± 0.35	−0.02 ± 0.60	0.38	0.38 ± 0.96	1.75 ± 1.23	0.003	0.22	< 0.001
V/AC	0.08 ± 0.17	0.01 ± 0.09	0.3	0.02 ± 0.36	−0.35 ± 0.29	0.012	0.31	0.012
Exercise stages	—	—		2.5 ± 0.8	3.8 ± 0.7	< 0.001		

Data presented are mean value ± SD. Abbreviations as in Table 1.

Table 3. Comparison of Changes in Various Hemodynamic Variables With Mental Stress and Exercise in Patients With a Mental Stress–Induced Fall in Left Ventricular Ejection Fraction (Group I) and Patients With No Fall in Left Ventricular Ejection Fraction (Group II)

	Mental Stress			Exercise		
Variable	Group I (n = 9)	Group II (n = 12)	p Value	Group I (n = 9)	Group II (n = 12)	p Value
LVEF (%)	−4 ± 3	−1 ± 2	0.02	−2 ± 12	1 ± 7	0.5
SV (ml)	−10 ± 6	0 ± 6	0.002	−4 ± 17	6 ± 16	0.18
HR (beats/min)	7 ± 4	8 ± 7	0.6	42 ± 28	51 ± 27	0.44
SBP (mm Hg)	15 ± 7	9 ± 9	0.12	15 ± 25	29 ± 20	0.18
DBP (mm Hg)	7 ± 7	3 ± 11	0.3	7 ± 11	4 ± 16	0.5
CO (liters/min)	−0.2 ± 0.4	0.6 ± 0.7	0.02	2.6 ± 3.1	4.9 ± 2.9	0.1
RPP (10^3, mm Hg/min)	2.2 ± 0.9	1.9 ± 1.2	0.6	8.5 ± 6.8	12.3 ± 6.7	0.23
PVR (dynes·s·cm^{-5})	252 ± 205	−42 ± 230	0.006	−382 ± 668	−671 ± 358	0.26
PP (W/ml)	0.2 ± 0.4	0.4 ± 0.7	0.4	1.0 ± 2.6	3.1 ± 2.4	0.025
SW (10^3, mm Hg/ml)	−0.39 ± 0.70	0.48 ± 1.01	0.03	0.57 ± 2.4	2.5 ± 2.6	0.08
E_a (mm Hg/ml)	0.41 ± 0.19	0.14 ± 0.29	0.02	0.30 ± 0.61	0.10 ± 0.29	0.6
E_{es} (mm Hg/ml)	0.17 ± 0.38	0.14 ± 0.34	0.6	0.29 ± 0.52	0.53 ± 1.16	0.4
V/AC	0.15 ± 0.24	0.04 ± 0.07	0.23	0.06 ± 0.47	0.62 ± 0.27	0.6
Exercise stages	—	—		2.1 ± 0.6	2.8 ± 0.7	0.02

Data presented are mean value ± SD. Abbreviations as in Table 1.

Comparison of Group I versus Group II patients with coronary artery disease. When comparing Group I patients with Group II patients, PVR increased significantly (252 ± 205 vs. −42 ± 230 dynes·s·cm^{-5}, p = 0.006), associated with a fall in SV (−10 ± 6 vs. 0 ± 6, p = 0.002) and a fall in CO (−0.2 ± 0.8 vs. 0.6 ± 0.7 liters/min, p = 0.003) in Group I compared with Group II. No difference was observed in heart rate, systolic and diastolic blood pressure, peak power and rate–pressure product (Table 3). Stroke work decreased in Group I and increased in Group II (p = 0.03). There was a greater increase in E_a in Group I compared with Group II (0.41 ± 0.19 vs. 0.14 ± 0.29, p = 0.02).

Group I and Group II versus normal subjects. Group I patients had a significant fall in LVEF (−4 ± 3% vs. 0 ± 4%, p = 0.008), an increase in PVR (252 ± 205 vs. −53 ± 149 dynes·s·cm^{-5}, p = 0.003), a decrease in CO (−0.2 ± 0.4 vs. 1.2 ± 0.9 liters/min, p = 0.001), a decrease in SV (−10 ± 6 vs. 3 ± 12, p = 0.02), a decrease in stroke work (−0.39 ± 0.7 vs. 1.5 ± 1.4, p = 0.003) and a greater increase in E_a (0.41 ± 0.19 vs. 0.05 ± 0.19, p = 0.001) compared with normal subjects. There were no significant differences in changes in systolic or diastolic blood pressure, peak power or the rate–pressure product. When comparing Group II patients with normal subjects, there was no significant change in any of the variables. Therefore, Group I patients accounted for the mental stress–induced differences observed between the patients with coronary artery disease and normal subjects.

Mental arithmetic versus anger recall. When comparing the two different mental stressors in patients with coronary artery disease, anger recall resulted in a greater fall in LVEF (−4 ± 4% vs. −1 ± 5%, p = 0.04), a greater increase in diastolic blood pressure (9 ± 13 vs. 1 ± 12 mm Hg, p = 0.04) and a greater increase in V/AC (0.2 ± 0.2 vs. 0.02 ± 0.22, p = 0.03) compared with mental arithmetic (Table 4). There was no difference in the changes in heart rate, SV, systolic blood pressure, PVR, peak power, stroke work, E_a and E_{es}.

In normal subjects, anger recall resulted in a fall in LVEF, whereas it increased with mental arithmetic (−4 ± 4% vs. 4 ± 5%, p = 0.01) (Table 4). Three normal subjects had a fall of ≥5% in LVEF with anger recall, whereas none had a fall of ≥5% in LVEF with mental arithmetic. Mental arithmetic resulted in a greater increase in heart rate (p = 0.004), a similar change in blood pressure, a greater increase in rate–pressure product (p = 0.005) and a greater increase in CO (p = 0.032) compared with anger recall. However, V/AC decreased with mental arithmetic, whereas it increased with anger recall (p = 0.006).

Changes in hemodynamic data with exercise. All normal subjects showed an increase in LVEF with exercise and none had chest pain, ST segment depression or wall motion abnormality.

With exercise there was no change in LVEF or SV in patients; heart rate increased (47 ± 28 beats/min), systolic (23 ± 23 mm Hg) and diastolic (5 ± 14 mm Hg) blood pressure increased, CO increased (3.9 ± 3.1 liters/min), rate–pressure product increased (10.7 ± 6.9 beats/min × mm Hg), PVR decreased (−547 ± 521 dynes·s·cm^{-5}), peak power increased (2.2 ± 2.3) and stroke work and E_{es} increased. E_a and V/AC changed minimally (Table 2). When comparing the exercise-induced changes between patients with coronary artery disease and normal subjects, there were significant differences in changes in LVEF, SV, heart rate, systolic and diastolic blood pressure, CO, rate–pressure product, peak power, stroke work, E_{es} and V/AC. There was no change in LVEF with exercise in patients, although this variable increased in normal subjects (p = 0.002). There was no increase in SV in patients, although this variable increased in normal subjects (p = 0.006). There was a greater increase in heart rate (p = 0.03), systolic blood

Table 4. Comparison of Changes in Various Hemodynamic Variables Between Two Different Mental Stressors in Patients and in Normal Subjects

Variable	Patients (n = 21)			Normal Subjects (n = 9)		
	Mental Arithmetic	Anger Recall	p Value	Mental Arithmetic	Anger Recall	p Value
LVEF (%)	−1 ± 5	−4 ± 4	0.04	4 ± 5	−4 ± 4	0.01
SV (ml)	−3 ± 14	−6 ± 11	0.5	9 ± 20	−4 ± 24	0.28
HR (beats/min)	7 ± 7	8 ± 8	0.5	17 ± 11	5 ± 6	0.004
SBP (mm Hg)	11 ± 12	13 ± 14	0.6	13 ± 8	10 ± 8	0.5
DBP (mm Hg)	1 ± 12	9 ± 13	0.04	7 ± 8	12 ± 9	0.28
CO (liters/min)	0.4 ± 1.1	0.1 ± 0.9	0.4	2.3 ± 1.7	0.1 ± 1.5	0.032
RPP (10^3, mm Hg/min)	1.8 ± 1.5	2.2 ± 1.5	0.4	2.7 ± 1.9	1.1 ± 1.3	0.005
PVR (dynes·s·cm^{-5})	−19 ± 355	186 ± 422	0.1	−126 ± 123	19 ± 233	0.089
PP (W/ml)	0.4 ± 0.8	0.2 ± 0.7	0.3	0.9 ± 1.2	−0.2 ± 2.2	0.14
SW (10^3, mm Hg/ml)	0.24 ± 2.2	0 ± 1.3	0.7	2.45 ± 3.05	0.54 ± 2.94	0.3
E_a (mm Hg/ml)	0.19 ± 0.41	0.3 ± 0.4	0.3	0.04 ± 0.23	0.06 ± 0.25	0.8
E_{es} (mm Hg/ml)	0.16 ± 0.52	0.1 ± 0.4	0.7	0.12 ± 0.95	−0.16 ± 0.33	0.3
V/AC	0.02 ± 0.22	0.2 ± 0.2	0.03	−0.09 ± 0.11	0.10 ± 0.10	0.006

Data presented are mean value ± SD. Abbreviations as in Table 1.

pressure ($p < 0.001$) and rate–pressure product ($p = 0.03$) in normal subjects compared with patients; however, there was no difference in diastolic blood pressure. There was a greater increase in CO ($p < 0.001$), peak power ($p < 0.001$), stroke work ($p < 0.001$) and E_{es} ($p = 0.003$) in normal subjects compared with patients. There was no difference in changes in PVR and E_a between the two groups. However, normal subjects exercised significantly longer than patients with coronary artery disease (3.8 ± 0.7 vs. 2.5 ± 0.8 stages of 3 min each, $p < 0.001$), which may account for most of these differences (Table 2).

Exercise responses in Group I and Group II. With exercise, 7 patients (33%) had a fall of ≥5% in LVEF, 8 (38%) had new transient wall motion abnormalities, 3 had angina and 4 had ≥1 mm ST segment depression. When comparing Group I with Group II patients, an exercise-induced fall of ≥5% in LVEF occurred in 4 patients (44%) in Group I and in 3 patients (25%) in Group II, and wall motion abnormalities occurred in 4 Group I patients (44%) and 4 Group II patients (33%). Angina occurred in 3 patients (33%) in Group I and none in Group II (all p = NS). ST segment depression occurred in 1 Group I patient (11%) and in 3 Group II patients (25%) (p = NS). The changes in heart rate, blood pressure, CO and PVR were not different between Group I and Group II patients (Table 3). There was greater increase in peak power (3.1 ± 2.4 vs. 1.0 ± 2.6 W/ml, $p = 0.025$) in Group II compared with Group I. However, Group II patients exercised longer than Group I patients (2.8 ± 0.7 vs. 2.1 ± 0.6 stages of 3 min each, $p = 0.02$).

Comparison between mental stress–induced and exercise-induced changes. Exercise compared with mental stress resulted in a significantly greater increase in heart rate ($p < 0.001$), a trend toward a greater increase in systolic blood pressure ($p = 0.06$), a similar increase in diastolic blood pressure, no difference in changes in SV and LVEF, a greater increase in CO ($p < 0.001$), rate-pressure product ($p < 0.001$), peak power ($p = 0.001$) and stroke work ($p = 0.02$) and lowering of PVR ($p < 0.001$) in patients with coronary artery disease (Table 2). There was no difference in E_a, E_{es} and V/AC. Unlike mental stress in patients with coronary artery disease, exercise in normal subjects resulted in a significantly greater increase in SV, LVEF and E_{es} and a greater lowering of VA/C. However, as mentioned previously, normal subjects exercised significantly longer than patients.

When comparing the changes in various hemodynamic variables with mental stress between seven patients with an exercise-induced fall in LVEF and the remaining 14 patients without an exercise-induced fall in LVEF, there were no differences in any of the variables (Table 5). Therefore, the LVEF response to exercise was not predictive of the LVEF response to mental stress.

Discussion

The results of this study indicate significant differences in vascular responses to mental stress between patients with coronary artery disease and healthy subjects, as well as between patients with CAD with and without mental stress–induced LV dysfunction. Mental stress resulted in comparable but relatively modest increases in heart rate and systolic and diastolic blood pressures in patients as well as in normal subjects. PVR and E_a increased in patients, although they decreased or remained unchanged in normal subjects, despite a similar change in heart rate and blood pressure. Changes in ventricular contractility in response to mental stress did not differ between patients with coronary artery disease and normal subjects, and stroke work and CO increased significantly in normal subjects as compared with patients with coronary artery disease.

Peripheral vasoconstrictive response. When we studied patients with coronary artery disease with and without a fall in LVEF with regard to mental stress, significant increases in PVR and E_a and a fall in SV, CO and stroke work were observed in the mental stress–positive group. In contrast, the changes in peak power and E_{es} did not differ. Mental stress did not produce ST segment depression and was accompanied by

Table 5. Comparison of Changes in Various Hemodynamic Variables With Mental Stress and Exercise in Patients With an Exercise-Induced Fall in Left Ventricular Ejection Fraction (Group A) and Patients With No Fall in Left Ventricular Ejection Fraction (Group B)

	Mental Stress			Exercise		
Variable	Group A (n = 7)	Group B (n = 14)	p Value	Group A (n = 7)	Group B (n = 14)	p Value
LVEF (%)	−3.5 ± 3	−1 ± 3	0.17	−10 ± 5	5 ± 7	< 0.001
SV (ml)	−8 ± 7	−3 ± 7	0.17	−8 ± 11	6 ± 17	0.04
HR (beats/min)	7 ± 6	8 ± 6	0.7	51 ± 33	43 ± 24	0.38
SBP (mm Hg)	13 ± 10	11 ± 8	0.77	27 ± 26	21 ± 22	0.6
DBP (mm Hg)	4 ± 10	5 ± 9	0.8	12 ± 11	2 ± 15	0.11
CO (liters/min)	0.1 ± 1.2	0.4 ± 0.8	0.43	3.7 ± 3.8	4.0 ± 2.8	0.87
DP (10^3, mm Hg/min)	2.1 ± 1.5	1.9 ± 0.8	0.7	13.0 ± 8.9	9.5 ± 5.6	0.38
PVR (dynes·s·cm^{-5})	142 ± 264	54 ± 264	0.15	−296 ± 516	−673 ± 493	0.15
PP (W/ml)	0.01 ± 0.75	0.43 ± 0.48	0.21	1.2 ± 2.1	2.7 ± 2.4	0.15
SW (10^3, mm Hg/ml)	−0.38 ± 0.84	0.36 ± 0.97	0.09	0.87 ± 2.8	1.98 ± 2.57	0.39
E_a (mm Hg/ml)	0.38 ± 0.30	0.19 ± 0.25	0.19	0.5 ± 0.3	0.03 ± 0.46	0.01
E_{es} (mm Hg/ml)	0.06 ± 0.46	0.17 ± 0.29	0.58	−0.4 ± 0.5	0.79 ± 0.89	0.001
V/AC	0.18 ± 0.20	0.03 ± 0.14	0.11	0.4 ± 0.2	−0.19 ± 0.23	< 0.001

Data presented are mean value ± SD. Abbreviations as in Table 1.

chest pain in only two patients. These suggest the potential primacy of peripheral vascular responses to mental stress in patients with coronary artery disease as one major (if not the major) mechanism responsible for the mental stress–induced fall in LVEF. This phenomenon may be due to increased levels of circulating catecholamines associated with mental stress (6,21). However, unlike exercise, the mental stress–induced fall in LVEF is early and a maximal response is often seen within minutes. This also suggests a possible additional role of central neurogenic-mediated vasoconstriction or a paradoxic vasoconstrictive response to normally occurring vasodilator stimuli.

Mental stress–versus exercise-induced LV dysfunction. A number of important differences have been noticed between mental stress–induced and exercise-induced LV dysfunction in patients with coronary artery disease. The mental stress–induced LVEF fall appears to occur with relatively smaller increases in heart rate and blood pressure and is seldom accompanied by ST segment depression or angina (1,2,6). Because LVEF is sensitive to afterload, a fall in LVEF could result from either a decrease in LV contractility or an increase in afterload, or a combination of these. Mental stress results in a greater increase in PVR and other indexes of afterload (6,21). Mental stress also causes a fall in LVEF in a minority of apparently healthy subjects. In our study, this was seen in 3 (33%) of 9 normal subjects. Becker et al. (21) observed a fall of ≥5% in LVEF during mental stress in 12 (41%) of 29 normal subjects aged 45 to 73 years (21). Even considering a more stringent criterion of ≥8% fall in LVEF, 5 (17%) of 29 subjects had abnormal findings (21). Similar findings have been observed in other studies (22). These data point to a significant peripheral vascular role in the mental stress–induced fall in LVEF, at least in normal subjects.

The role of ischemia in a mental stress–induced fall in LVEF cannot, however, be dismissed completely. Transient wall motion and reversible perfusion abnormalities have been observed during mental stress in patients with coronary artery disease (2,3,23,24). In the present study, several patients developed new wall motion abnormalities during mental stress. The development of transient wall motion abnormalities is generally considered to be more specific for myocardial ischemia. However, Becker et al. (21) also recently observed transient wall motion abnormalities during mental stress in 3 (7%) of 41 healthy subjects. We did not observe transient wall motion abnormalities with mental stress in any of our normal subjects.

Myocardial perfusion with mental stress in patients with coronary artery disease. Giubbini et al. (23) observed mental stress–induced reversible perfusion defects in patients with coronary artery disease. These perfusion abnormalities were seen in the same zones where exercise-induced perfusion abnormalities were seen. Deanfield et al. (24) observed similar findings using positron emission tomography. Yeung et al. (25) observed paradoxic vasoconstriction in large, diseased epicardial coronary vessels during coronary angiography in response to mental arithmetic. This vasoconstrictive response was similar to the paradoxic coronary vasoconstriction noted with intracoronary acetylcholine administration. Intracoronary Doppler flow imaging and intracoronary acetylcholine administration also showed an absolute drop in coronary blood flow in these patients with mental stress (25), thereby suggesting a process of coronary vasoconstriction in coronary artery disease during mental stress. L'Abbate et al. (26) found a decrease in coronary blood flow in patients with coronary artery disease with mental stress despite no change in lumen diameter at the site of the atherosclerotic lesion, raising the possibility that the vasoconstriction was microvascular (26).

We also observed evidence of an abnormal increase in PVR and E_a in patients with coronary artery disease who developed a fall in LVEF in response to mental stress. PVR is an index of the nonpulsatile component of afterload, assuming a nonpulsatile or constant blood flow through the arterial system. E_a takes into account both pulsatile and nonpulsatile components

(19). To explain further, at a given mean arterial pressure and CO, PVR would remain constant over a wide range of heart rates; however, E_a would differ at different heart rates, being lower at lower heart rates and higher at higher heart rates. This distinction is important when studying the impact of interventions on afterload that result in changes in blood pressure as well as heart rate.

Peripheral vasoconstriction as a possible marker of coronary vasoconstriction. We did not observe a decrease in peak power or E_{es} with mental stress in patients with coronary artery disease. This suggests no major change in contractility. Alternatively, there may be an inadequate increase in contractility to match the acute increase in afterload. Although peak power and E_{es} are reliable indexes of LV contractility, relatively independent of afterload, these indexes have mostly been used to study increases in LV contractility or contractile reserve with positive interventions such as exercise or inotropic stimulation.

Although not evaluated in the current study, it is possible that abnormal increases in PVR and E_a are also accompanied by similar changes in the coronary circulation. If this mechanism is operative, the fall in LVEF and regional wall motion abnormalities could be due to vasoconstrictive responses in both peripheral and coronary microcirculation. In this context, changes in PVR and E_a could be systemic markers of abnormal coronary vasomotor responses. It is not known whether this would occur at the site of atherosclerotic narrowing or at the microvascular level, or both, and whether this is humorally mediated or a neurogenic vasoconstrictive response. The rapidity with which a fall in LVEF occurs in response to mental stress is more suggestive of neurogenic vasoconstrictive response.

Anger recall versus mental arithmetic. Of the two mental stressors used in this study, anger recall was more potent in inducing a fall in LVEF. Goldberg et al. (6) observed that the speech test, a test somewhat similar to anger recall, resulted in greater changes in blood pressure and catecholamine levels and greater ischemia compared with the color Stroop test. However, in both studies, a small percentage of patients developed a fall in LVEF or wall motion abnormalities in response only to the relatively "weaker" mental stressor. Therefore, continued use of a battery of mental stressors rather than a single stressor appears justified.

Exercise versus mental stress–induced fall in LVEF. Exercise-induced changes in LVEF and other hemodynamic indexes were not predictive of changes with mental stress. Of the seven patients who developed a ≥5% fall in LVEF with exercise, only four did so with mental stress. Similarly, only four of nine patients with a mental stress–induced fall in LVEF did so with exercise. There were no differences in any of the hemodynamic variables associated with mental stress between patients with and without an exercise-induced fall in LVEF. These findings are similar to those of Goldberg et al. (6). These findings are different from those obtained by Holter monitoring in which silent myocardial ischemia has been observed to correlate with the severity of exercise-induced myocardial ischemia (27). These differences also suggest different mechanisms for the changes in LV function with mental stress and with exercise.

Study limitations. Although the afterload-insensitive nature of cardiac peak power is well established, it is not known whether this is sensitive enough to detect small changes in LV contractility. Furthermore, antianginal and antihypertensive medications were continued during the study. The hemodynamic effects of these medications may have affected our results. However, despite continuation of these medications, we observed a fall in LVEF in response to mental stress in 44% of our patients. In a previous study, we observed a LVEF fall in 50% of patients with coronary artery disease, while they were taking routine medications (1). A mental stress–induced fall in LVEF in nearly half of patients with coronary artery disease, despite antianginal therapy, further supports the peripheral vasoconstrictive response as being primarily responsible for this phenomenon. Whether a greater proportion of patients would have a LVEF fall after withdrawal of antianginal therapy remains speculative. In a recent pilot study, addition of a long-acting calcium channel blocking agent did not change the mental stress–induced fall in LVEF, despite a significant improvement in exercise capacity and exercise-induced ischemia (28). Goldberg et al. (6) noted that 58% of patients with coronary artery disease had evidence of myocardial ischemia with mental stress after their antianginal medications were discontinued.

Clinical implications. Stress-related phenomena such as an earthquake, war or threat of attack are known to be associated with several-fold higher occurrences of myocardial infarction and cardiac death (29,30). In these settings, as well as in normal life, mental stress, anger and certain behavioral traits are emerging as important contributing factors toward adverse cardiac events in patients with coronary artery disease (31,32). Mechanistically, patients with coronary artery disease who show a fall in LVEF in response to mental stress manifest peripheral vasoreactivity and perhaps also abnormal coronary vasoreactivity to mental stress. This abnormal vasoreactivity to mental stress and other unidentified stimuli may relate to the vulnerability of patients with a mental stress–induced fall in LVEF to adverse cardiac events (7,8). Different therapeutic approaches from those currently used for exercise-induced myocardial ischemia may be required to deal with mental stress–induced LV dysfunction in susceptible groups of patients with coronary artery disease. In addition, mental stress testing could become a part of the comprehensive evaluation of susceptible patients with coronary artery disease.

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References

1. Burg MM, Jain D, Soufer R, Kerns RD, Zaret BL. Role of behavioral and psychological factors in mental stress–induced silent left ventricular dysfunction in coronary artery disease. J Am Coll Cardiol 1993;32:440–8.
2. Rozanski A, Bairey N, Krantz D, et al. Mental stress and the induction of

silent myocardial ischemia in patients with coronary artery disease. N Engl J Med 1988;318:1005–12.
3. La Veau P, Rozanski A, Krantz D, et al. Transient left ventricular dysfunction during provocative mental stress in patients with coronary artery disease. Am Heart J 1989;118:1–6.
4. Ironson G, Taylor CB, Boltwood M, et al. Effects of anger on left ventricular ejection fraction in coronary artery disease. Am J Cardiol 1992;70:281–5.
5. Specchia G, de Servi S, Falcone C, et al. Mental arithmetic stress testing in patients with coronary artery disease. Am Heart J 1984;108:56–63.
6. Goldberg AD, Becker LC, Bonsall R, et al. Ischemic, hemodynamic, and neurohormonal response to mental stress and exercise stress: experience from the Psychophysiological Investigations in Myocardial Ischemia (PIMI) study. Circulation 1996;94:2402–9.
7. Jain D, Burg M, Soufer R, Zaret BL. Prognostic implications of mental stress–induced silent left ventricular dysfunction in patients with stable angina pectoris. Am J Cardiol 1995;76:31–5.
8. Jiang W, Babyak M, Krantz DS, et al. Mental stress–induced myocardial ischemia and cardiac events. JAMA 1996;275:1651–6.
9. Massardo T, Gal RA, Grenier RP, Schmidt DH, Port SC. Left ventricular volume calculation using a count-based ratio method applied to multigated radionuclide angiography. J Nucl Med 1990;31:450–6.
10. Marmor A, Jain D, Cohen LS, Nevo E, Wackers JThF, Zaret BL. Left ventricular peak power during exercise: a noninvasive approach for assessment of contractile reserve. J Nucl Med 1993;34:1877–85.
11. Sharir T, Marmor A, Ting C, et al. Validation of a method for noninvasive measurement of central arterial pressure. Hypertension 1993;21:74–82.
12. Haber HL, Simek CL, Bergin JD, et al. Bolus intravenous nitroglycerin predominantly reduces afterload in patients with excessive arterial elastance. J Am Coll Cardiol 1993;22:251–7.
13. Colston JT, Freeman G. Beneficial influence of vasoactive intestinal peptide on ventriculovascular coupling in closed-chest dogs. Am J Physiol 1992;263: H1300–5.
14. Hayshida K, Sunagawa K, Noma M, Sugumachi M, Ando H, Nakamura M. Mechanical matching of the left ventricle with the arterial system in exercising dogs. Circ Res 1992;71:481–9.
15. Marmor A, Jain D, Zaret BL. Beyond ejection fraction. J Nucl Cardiol 1994;1:477–86.
16. Callahan RJ, Froelich JW, McKusick KA, Leppo J, Strauss HW. A modified method for the in vivo labeling of red blood cells with Tc-99m: concise communication. J Nucl Med 1982;23:315–8.
17. Lee FA, Fetterman R, Zaret BL, Wackers FJTh. Rapid radionuclide derived systolic and diastolic cardiac function using cycle-dependent background correction and Fourier analysis. In: Proceedings of Computers in Cardiology. Linkoping, Sweden: IEEE Computer Society, 1985:443–6.
18. Marmor AT, Blondheim DS, Gozlan E, Navo E, Front D. Method for noninvasive measurement of central aortic systolic pressure. Clin Cardiol 1987;10:215–21.
19. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513–21.
20. Asanoi H, Sasayama S, Kameyama T. Ventriculoarterial coupling in normal and failing heart in humans. Circ Res 1989;65:483–93.
21. Becker LC, Pepine CJ, Bonsall R, et al. Left ventricular, peripheral vascular, and neurohumoral responses to mental stress in normal middle-aged men and women: reference group for the Psychophysiological Investigations in Myocardial Ischemia (PIMI) study. Circulation 1996;94:2768–77.
22. Tamaki N, Gill JB, Moore RH, Yasuda T, Boucher CA, Strauss HW. Cardiac response to daily activities and exercise in normal subjects assessed by an ambulatory ventricular function monitor. Am J Cardiol 1987;59: 1164–9.
23. Giubbini R, Galli M, Campini R, Bosimini E, Bencivelli W, Tavazzi L. Effects of mental stress on myocardial perfusion in patients with ischemic heart disease. Circulation 1991;83 Suppl II:II-100–7.
24. Deanfield JE, Shea M, Kensett M, et al. Silent myocardial ischemia due to mental stress. Lancet 1984;2:1001–5.
25. Yeung AC, Vekshtein VI, Krantz DS, et al. The effects of atherosclerosis on the vasomotor response of coronary arteries to mental stress. N Engl J Med 1991;325:1551–6.
26. L'Abbate A, Simonetti I, Carpeggiani C, Michelassi C. Coronary dynamics and mental arithmetic stress in humans. Circulation 1991;83 Suppl II:II-94–9.
27. Deanfield JE, Maseri A, Selwyn AP, et al. Myocardial ischemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 1983;2:753–8.
28. Jain D, Burg M, Soufer R, Zaret BL. Discordant effects of amlodipine on exercise-induced vs. mental stress–induced myocardial ischemia in patients with angina [abstract]. J Nucl Med 1996;37:59P.
29. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med 1996;334:418–9.
30. Meisel SR, Kutz I, Dayan KI, et al. Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. Lancet 1991;338:660–1.
31. Gullette EC, Blumenthal JA, Babyak M, et al. Effects of mental stress on myocardial ischemia during daily life. JAMA 1997;277:1521–6.
32. Mittleman MA, Machera M. Mental stress during daily life triggers myocardial ischemia [editorial]. JAMA 1997;277:1558–9.