Effect of Mental Stress on Myocardial Blood Flow and Vasomotion in Patients with Coronary Artery Disease

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In patients with coronary artery disease (CAD), mental stress may provoke ischemic electrocardiograph changes and abnormalities in regional and global left ventricular function. However, little is known about the underlying myocardial blood flow response (MBF) in these patients. **Methods:** We investigated the hemodynamic, neurohumoral, and myocardial blood flow responses to mental stress in 17 patients with CAD and 17 healthy volunteers of similar age. Mental stress was induced by asking individuals to solve mathematic subtractions in a progressively challenging sequence; MBF was quantified at rest and during mental stress using ^{13}N ammonia PET. **Results:** Mental stress induced significant ($P < 0.01$) and comparable increases in rate–pressure product, measured in beats per minute × mm Hg, in both patients (from 7826 ± 2006 to 10586 ± 2800) and healthy volunteers (from 8227 ± 1272 to 10618 ± 2468). Comparable increases also occurred in serum epinephrine (58% in patients versus 52% in healthy volunteers) and norepinephrine (22% in patients versus 27% in healthy volunteers). Although MBF increased in patients (from 0.67 ± 0.15 to 0.77 ± 0.18 mL/min/g, $P < 0.05$) and healthy volunteers (from 0.73 ± 0.13 to 0.95 ± 0.22 mL/min/g, $P < 0.001$), the magnitude of flow increase was smaller in patients (14% ± 17%) than in healthy volunteers (29% ± 14%) ($P = 0.01$). The increase in MBF during mental stress correlated significantly with changes in cardiac work in healthy volunteers ($r = 0.77$; $P < 0.001$) but not in patients. **Conclusion:** Despite similar increases in cardiac work and comparable sympathetic stimulation in CAD patients and healthy volunteers, CAD patients exhibit an attenuated blood flow response to mental stress that may contribute to mental stress–induced ischemic episodes in daily life.

Key Words: mental stress; myocardial blood flow; PET

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The normal cardiovascular response to mental stress involves increases in heart rate, blood pressure and cardiac contractility (*1,2*). The corresponding increase in myocardial oxygen demand is physiologically accommodated by an increase in myocardial blood flow (MBF). Therefore, in healthy individuals mental stress induces coronary artery vasodilatation (*3,4*). In patients with coronary artery disease (CAD), however, mental stress modeled in a laboratory or experienced in daily life can induce myocardial ischemia as evidenced by ischemic changes on electrocardiography (ECG) (*5*), left ventricular wall motion abnormalities, and a decline in left ventricular ejection fraction (*6,7*). Such abnormal responses to mental stress may also predict ischemic events, such as unstable angina pectoris or myocardial infarction, in daily life (*8,9*).

The mechanisms underlying these mental stress–induced alterations in cardiac function are poorly understood. Yeung et al. (*4*) observed a significant association between the endothelium-dependent coronary vasomotor response to intracoronary acetylcholine and that to mental stress in patients with CAD. This association suggested that endothelial dysfunction may account for the inadequate MBF response to mental stress. However, the MBF response to mental stress has not, to our knowledge, been studied systematically. Therefore, our aim was to quantify noninvasively, with dynamic PET, the MBF response to mental stress in patients with CAD.

MATERIALS AND METHODS

Study Population

The study population comprised 17 patients with documented CAD (11 men, 6 women; age range, 45–76 y; mean age [±SD], 63 ± 11 y) and 17 healthy volunteers with a low probability for CAD (8 men, 9 women; age range, 40–74 y; mean age, 57 ± 11 y). The age difference between the two groups was not statistically significant (NS). All patients had stable CAD, and none had undergone coronary artery bypass surgery. CAD was documented by coronary angiography in 14 patients, a myocardial stress or rest perfusion test in 5, and a history of a previous myocardial infarction in 6. Nine patients had a history of hypercholesterolemia (but cholesterol levels were normal on the day of the test), 6 had hypertension, 2 had a remote history of cigarette smoking, and 1 had type II diabetes mellitus. Three patients were treated with angiotensin-converting enzyme (ACE) inhibitors; 9, with β-block-

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ers; 2, with calcium antagonists; 6, with β-3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; 1, with oral antidiabetic agents; and 1, with diuretics. All β-blockers and calcium channel blockers were discontinued 24 h before PET was performed.

A low probability for CAD in the healthy volunteers was based on absence of anginal symptoms, normal findings on resting ECG, and absence of cardiovascular risk factors (*10*); all healthy volunteers were nonsmokers, and none had a history of hypertension, diabetes mellitus, or familial hyperlipidemia. In addition, all participants more than 50 y old underwent a treadmill test that revealed no evidence of CAD.

Each participant signed an informed consent form approved by the Human Subject Protection Committee.

Study Protocol

MBF was quantified at baseline and during mental stress with ^{13}N ammonia and PET. For baseline measurements, 555–740 MBq (15–20 mCi) ^{13}N ammonia were injected intravenously and transaxial images were acquired in a sequence consisting of 12 image frames of 10 s each, 2 frames of 30 s each, and 1 frame of 900 s. During and after this baseline study, the room lights were dimmed, background noise was minimized, and participants were encouraged to relax. Forty-five minutes afterward (to allow for radioactive decay of ^{13}N ammonia), mental stress was induced for 7 min using a standardized mental stress protocol (*2*). In brief, each participant was asked to serially subtract a 1- or 2-digit number from a 4-digit number. Every 2 min, the problem was made more difficult and the time to solve it was shortened. After an initial increase in heart rate and blood pressure, a stable plateau in hemodynamic response was consistently observed at minute 2 or 3 of the mental stress protocol. At that time, a second dose of ^{13}N ammonia (555–740 MBq) was injected and the mental stress protocol was continued for another 4–5 min, i.e., 7 min total. Heart rate, arterial blood pressure (measured by an automated blood pressure cuff), and 12-lead ECG findings were recorded at 1-min intervals throughout the test; during application of mental stress the ECG findings were recorded continuously. The rate–pressure product was calculated to obtain an index of cardiac work (*11*).

Venous blood samples for determination of plasma glucose, serum cholesterol, and triglyceride levels were taken before the study. In addition, venous blood samples for serum epinephrine and norepinephrine were drawn at rest (10 min before stress) and during mental stress to evaluate the neurohumoral response.

PET

A whole-body ECAT/EXACT positron emission tomograph (CTI/Siemens, Knoxville, TN), which acquires 63 image planes simultaneously, was used. The tomograph has a 15-cm axial field of view and an intrinsic in-plane resolution of 3.6 mm full width at half maximum (*12*). The images were reconstructed using a Hanning filter with a cutoff frequency of 0.4 cycles per pixel, resulting in an effective in-plane resolution of 10 mm. A 20-min transmission scan was obtained first for correction of photon attenuation, followed by measurement of MBF as described above.

Visual and Semiquantitative PET Image Analysis

The transaxially acquired image sets were reoriented into horizontal and vertical long-axis and short-axis views of the left ventricle. Images were analyzed visually for presence (reversible or fixed) or absence of perfusion defects by 2 physicians unaware of clinical and PET data. The short-axis images were composed and displayed as polar maps of the relative myocardial ^{13}N ammonia distribution. Normal resting perfusion was defined as a ^{13}N ammonia uptake within 2 SDs of the mean of a normal database previously established at our institution (*13*). Polar maps of the mental stress findings were normalized to the peak 5% of activity within each map because a normal database for the MBF response to mental stress had not been established.

Quantification of MBF

Regional MBF at rest and during mental stress was quantified in the vascular territories of the left anterior descending, left circumflex, and right coronary arteries. Sectors of interest ranging from 70° to 90° were placed in one basal, one midventricular, and one apical short-axis slice of the left ventricle. A small region of interest (25 mm^2) was centered in the left ventricular blood pool to derive the arterial input function (*14*). These regions were then copied to the serially acquired images, and regional myocardial time–activity curves were obtained. For each vascular territory, a single time–activity curve was derived by averaging the time activity data from three short-axis images.

Partial-volume effects were corrected for using a recovery coefficient of 0.73 that assumes a uniform left ventricular wall thickness of 1 cm. Both the blood pool and the myocardial time–activity curves were corrected for physical decay of ^{13}N ammonia and were fitted with a previously validated two-compartment tracer kinetic model that corrects for activity spillover from the blood pool into the left ventricular myocardium (*15,16*).

Serum Lipid and Catecholamine Measurements

Total serum cholesterol and high-density lipoprotein cholesterol were measured using standard enzymatic methods. Low-density lipoprotein cholesterol was calculated using the formula of Friedewald et al. (*17*). Serum epinephrine and norepinephrine were measured using high-performance liquid chromatography (*18*).

Statistical Analysis

Data are presented as mean values with SD. Comparisons within groups were performed using a Student t test for paired data; comparisons between groups used t testing for unpaired data. Correlations were sought using the least squares method. Possible differences in the magnitude of blood flow and hemodynamic response to mental stress between groups were evaluated using a two-sample Mann-Whitney test. $P < 0.05$ was considered statistically significant.

RESULTS

Hemodynamic and Clinical Findings

Table 1 summarizes hemodynamic findings. The resting rate–pressure product, measured in beats per minute × mm Hg, was similar (P = NS) in healthy volunteers (8227 ± 1272) and patients (7826 ± 2006). During mental stress, the product increased by 27% ± 11% in healthy volunteers and 33% ± 16% in patients (P = NS between groups and $P <$ 0.01 versus baseline in each group). In 1 patient, slight chest pain and horizontal 0.10-mV ST segment depression developed immediately after stress testing. The remaining patients did not exhibit ECG changes or clinical signs suggestive of myocardial ischemia.

Semiquantitative Analysis

The vascular territories numbered 102—51 each (17 × 3) in healthy volunteers and patients. In healthy volunteers,

TABLE 1
Hemodynamic Parameters at Rest and During Mental Stress

Parameter	Patients		Healthy volunteers	
	Rest	Mental stress	Rest	Mental stress
Heart rate (beats/min)	61 ± 11	68 ± 13*	69 ± 9	77 ± 10*
Systolic blood pressure (mm Hg)	127 ± 18	155 ± 23*	123 ± 20	138 ± 25*
Diastolic blood pressure (mm Hg)	70 ± 7	82 ± 8*	74 ± 7	81 ± 9*
Mean arterial blood pressure (mm Hg)	89 ± 10	106 ± 11*	90 ± 10	100 ± 14*
Rate pressure product	7826 ± 2006	10586 ± 2800*	8227 ± 1272	10618 ± 2468*

*$P < 0.001$ for measurements during mental stress versus rest.
Data during mental stress and rest are not different between patients and healthy volunteers.

visual and polar map analysis showed that tracer uptake in all 51 vascular territories was normal and homogeneous. In patients, 43 vascular territories showed normal tracer uptake, 2 showed stress-induced perfusion defects, and 6 showed fixed (rest and stress) perfusion defects. Fixed defects corresponded to areas of clinically documented myocardial infarction, and blood flow in these areas was analyzed separately.

MBF at Rest and During Mental Stress

The following data pertain to 51 vascular territories in healthy volunteers and 45 territories in patients (i.e., 43 territories with a normal polar map and two with reversible perfusion defects). At baseline, MBF was similar (P = NS) in patients (0.67 ± 0.15 mL/min/g) and healthy volunteers (0.73 ± 0.13 mL/min/g). In both groups, MBF did not differ (P = NS) between vascular territories of the left anterior descending artery, left circumflex artery, and right coronary artery (in patients, 0.67 ± 0.21, 0.78 ± 0.19, and 0.60 ± 0.16 mL/min/g, respectively; in healthy volunteers, 0.70 ± 0.13, 0.80 ± 0.15, and 0.68 ± 0.13 mL/min/g, respectively).

Mental stress induced an increase in MBF in both patients (from 0.67 ± 0.15 to 0.77 ± 0.18 mL/min/g, $P < 0.05$) and healthy volunteers (from 0.73 ± 0.13 to 0.95 ± 0.22 mL/min/g, $P < 0.001$). However, the magnitude of flow increase was significantly greater (P = 0.01) in healthy volunteers (29% ± 14%) than in patients (14% ± 17%) despite similar increases in the rate–pressure product (29% ± 11% in healthy volunteers and 33% ± 16% in patients, P = NS; Fig. 1). In patients the blood flow increase during mental stress was similarly attenuated in the territories of the left anterior descending, left circumflex, and right coronary arteries. To correct for individual differences in the hemodynamic response to mental stress, MBF was normalized to the rate–pressure product. At baseline, the normalized blood flow was similar in patients and healthy volunteers. With mental stress it declined from 0.86 ± 0.17 to 0.73 ± 0.18 in patients ($P < 0.001$) but remained unchanged in healthy volunteers (0.87 ± 0.13 before stress versus 0.90 ± 0.14 after stress; Fig. 2).

In the six vascular territories with fixed perfusion defects, MBF did not increase during mental stress (0.59 ± 0.18 mL/min/g before stress versus 0.61 ± 0.15 mL/min/g after stress).

Changes in MBF from baseline with mental stress correlated significantly with changes in the rate–pressure product in healthy volunteers (r = 0.77; P = 0.0003) but not in patients (r = 0.40; P = 0.10).

Coronary Vascular Resistance

Coronary vascular resistance was calculated as the ratio of mean arterial blood pressure to mean MBF (*19*). At baseline, coronary vascular resistance was similar in patients (territories with normal polar map and reversible perfusion defects: 138 ± 28 mm Hg/mL/min/g) and healthy volunteers (127 ± 21 mm Hg/mL/min/g). During mental stress the resistance declined significantly in healthy volunteers (to 109 ± 18 mm Hg/mL/min/g, $P < 0.001$) but remained unchanged in patients (145 ± 35 mm Hg/mL/min/g, P = NS versus baseline and P = 0.002 versus healthy volunteers during stress). In the 6 territories with a fixed perfusion defect,

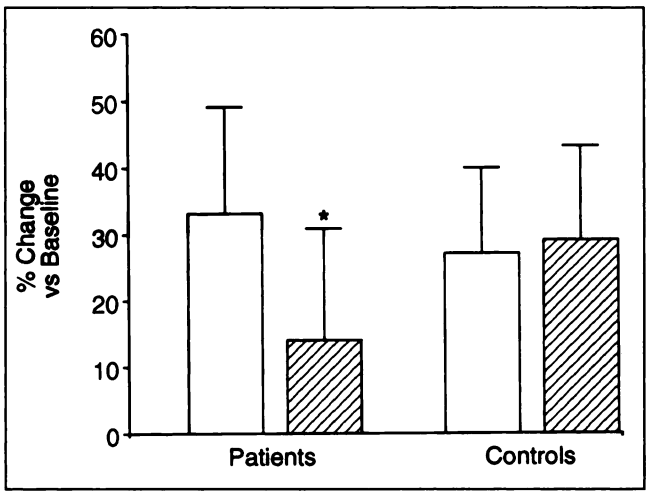

FIGURE 1. Magnitude of increase in cardiac work (rate–pressure product, white bars) and MBF (shaded bars) during mental stress in patients and healthy volunteers. Despite similar mental stress–induced increases in cardiac work, MBF increased significantly less in patients than in healthy volunteers. * = probability value of 0.01 versus controls.

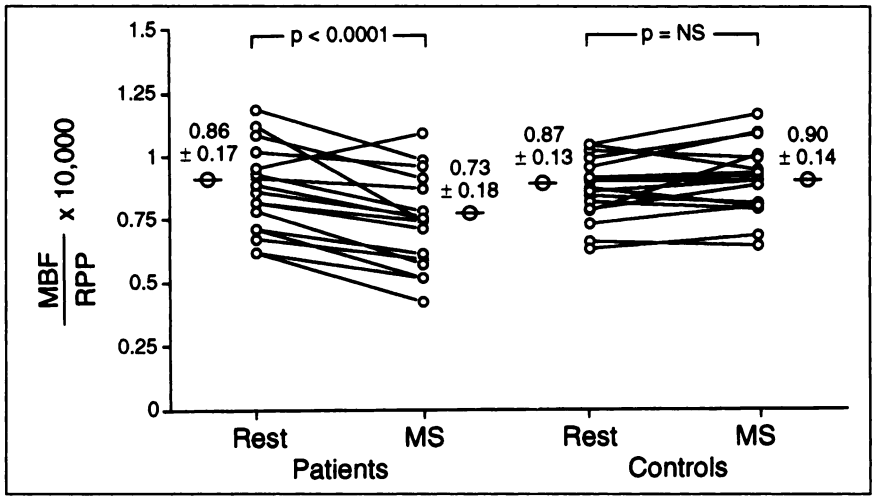

FIGURE 2. Mental stress–induced changes in myocardial blood flow (MBF) normalized to cardiac work. During mental stress (MS) normalized blood flow declined in patients but remained unchanged in healthy volunteers. NS = not statistically significant; RPP = rate pressure product.

which were again analyzed separately, coronary resistance remained unchanged (154 ± 41 versus 170 ± 41 mL/min/g/mm Hg; P = NS).

Serum Measurements

Table 2 lists serum concentrations for epinephrine and norepinephrine. Patients and healthy volunteers showed a similar increase (P = NS) in epinephrine and norepinephrine in response to mental stress. Serum lipid levels did not differ (P = NS) between patients and healthy volunteers (180 ± 33 versus 192 ± 26 mg/dL for total cholesterol, 107 ± 31 versus 125 ± 36 mg/dL for low-density lipoprotein cholesterol, and 37 ± 10 versus 44 ± 10 mg/dL for high-density lipoprotein cholesterol for patients and healthy volunteers, respectively) and were unrelated to the MBF response to mental stress.

DISCUSSION

Mental stress, although producing smaller increases in heart rate and blood pressure than does physical exercise, can induce myocardial ischemia in susceptible patients with CAD (*9,20,21*). The pathophysiologic mechanisms underlying this abnormal response to mental stress are still being investigated. Previous studies using mental stress testing in CAD patients have mainly focused on the left ventricular functional response to mental stress and have reported stress-induced wall motion abnormalities and a decline in the left ventricular ejection fraction (*6,7*). However, changes in left ventricular function are influenced by several factors, including catecholamine stimulation, MBF, and loading conditions. Some studies reported mental stress–induced perfusion defects (*20,22*), but the blood flow response to mental stress has never, to our knowledge, been quantified.

In this study, mental stress induced a comparable neurohumoral and hemodynamic response in CAD patients and healthy volunteers. However, the mental stress–induced increase in cardiac work was accommodated by a proportional increase in MBF only in healthy volunteers; patients exhibited an attenuated flow response. These findings might contribute to the understanding of pathophysiologic mechanisms involved in the development of mental stress–induced ischemia, because they indicate an uncoupling between stress-induced increases in cardiac work (and, therefore, oxygen demand) and changes in MBF.

TABLE 2
Serum Epinephrine and Norepinephrine at Rest and During Mental Stress

Serum component (pg/mL)	Patients		Healthy volunteers	
	Rest	Mental stress	Rest	Mental stress
Epinephrine	36 ± 12	57 ± 21*	29 ± 17	44 ± 16
Norepinephrine	289 ± 111	352 ± 140*	258 ± 124	327 ± 167*

*P < 0.01 for measurements during mental stress versus rest.

Pathophysiologic Mechanisms

Mental stress, like other sympathetic stimuli or physical exercise, induces a release of catecholamines from terminal cardiac nerve endings and from the adrenal medulla (*23*). In the coronary as well as the peripheral circulation, the vasomotor response to mental stress and to acetylcholine correlate closely, suggesting that the abnormal vasomotor response to mental stress is related to endothelial dysfunction and a reduced availability of endothelium-derived relaxing factor (nitric oxide) (*4,24,25*). For instance, in angiographically smooth coronary segments, mental stress was associated with vasodilatation or no change in the epicardial artery diameter, whereas any degree of angiographically detectable atherosclerosis was associated with coronary vasoconstriction (*4*). In addition, administration of the nitric oxide synthetase inhibitor *N*-monomethyl-L-arginine significantly blunted the normal blood flow increase in response to mental stress (*24,25*). Thus, nitric oxide release from intact endothelium contributes to the physiologic rise in blood flow during mental stress. In contrast,

damaged endothelium responds to stress-induced increases in circulating catecholamines with an increase in coronary vasomotor tone (*3,26*).

The attenuated blood flow response to mental stress observed in this study might therefore be related to an unopposed, and thus relatively enhanced, vasoconstrictor response to circulating catecholamines (*26*). Accordingly, despite comparable increases in cardiac work, only healthy volunteers showed proportional increases in cardiac work and MBF during mental stress, whereas in patients the stress-induced increase in blood flow was significantly blunted. However, although the MBF response to mental stress was blunted, it was not completely abolished. This finding suggests that other, endothelium-independent vasodilators, such as adenosine, may contribute to the regulation of coronary flow during mental stress (*27*).

The attenuated blood flow response to sympathetic stimulation (mental stress or cold pressor test) or intracoronary administration of acetylcholine can be attributed largely to abnormal vasomotion at the level of the coronary resistance vessels (*4,28,29*). In this study, coronary vascular resistance decreased during mental stress in healthy volunteers but not in patients, despite similar increases in cardiac work, indicating increased coronary vasomotor tone in patients. Similar findings were reported by Dakak et al. (*3*), who assessed coronary blood flow velocity during mental stress in patients with mild CAD. In their study, as in this study, coronary resistance declined in healthy volunteers but not in patients. However, resistance did decrease in patients when mental stress testing was repeated after intracoronary administration of phentolamine, indicating an unopposed α-adrenoreceptor activation in microvascular smooth muscle cells (*3*). Other sympathetic stimuli, such as the cold pressor test, also induce coronary vasoconstriction in patients with risk factors for or clinically manifest CAD (*30*), and this paradoxic vasoconstriction can be attenuated by α_1-receptor blockade (*31*).

Alternatively, the abnormal MBF response to mental stress may be related to alterations in the sympathetic innervation of the coronary vasculature. Abnormal coronary sympathetic innervation has been shown after cardiac transplantation, after myocardial infarction, and in patients with cardiomyopathy (*32,33*). However, in this study all patients had stable CAD and normal left ventricular function. In addition, territories with previous myocardial infarction were analyzed separately. Thus, inhomogeneities in cardiac innervation are unlikely to explain the abnormal MBF response to mental stress in CAD patients.

Methodologic Considerations

Mental stress may induce coronary vasoconstriction in patients with CAD (*4,34*). Thus, ischemic episodes during mental stress could be accounted for by both moderate increases in myocardial oxygen demand (increased cardiac work) and reductions in myocardial oxygen supply (vasoconstriction or lack of vasodilatation). In this study, the absolute changes in MBF were modest, but differences were significant between patients and healthy volunteers despite similar increases in the rate–pressure product. Chest pain developed in only 1 patient, and 2 patients exhibited reversible perfusion defects. These findings are not surprising: Blunted blood flow increase during mental stress occurred in all three vascular territories, and the resulting balanced reductions could not be detected by relative perfusion imaging. The lack of clinical evidence for myocardial ischemia, in turn, might be accounted for by two factors. First, previous studies observed an average oxygen extraction of only 66% at rest in normal myocardium of patients with cardiac disease (*35*). Thus, an increase in oxygen extraction might suffice to compensate for the attenuated flow increase during mental stress. Second, mental stress induces only a moderate increase in cardiac work. The increase is smaller than that caused by, for instance, treadmill testing (*23,36*). However, mental stress or other sympathetic stimuli are not designed or used for the detection of CAD. Rather, these tests provide an alternative, noninvasive means to probe coronary vasomotion (*4,30*). Finally, the observation that clinical or ECG signs of myocardial ischemia during mental stress develop in only a subset of patients also agrees with findings from a recent multicenter study (*36*).

Study Limitations

This study has some limitations. First, 3 patients were treated with ACE inhibitors, which have been shown to improve coronary endothelial dysfunction (*37*). Therefore, the true degree of coronary endothelial dysfunction in these patients may have been underestimated. However, no differences were observed in the blood flow response to mental stress between patients receiving and not receiving medication. Thus, a significant effect of ACE inhibition on coronary vasomotion was not apparent.

Although all 17 patients had documented CAD, the angiographic extent of the disease was assessed in only 14 patients (3–24 mo before PET). The actual extent and degree of atherosclerosis in most patients at the time of PET were therefore unknown, and the effects of stenosis severity on the MBF response to mental stress could not be addressed.

Finally, CAD could have been ruled out with certainty in the healthy volunteers only by coronary angiography. Performing such an invasive study was considered ethically unacceptable. However, all healthy volunteers had a pretest probability for CAD of less than 5% based on the established criteria of Diamond and Forrester (*10*). In addition, normal findings from treadmill ECG were required in all healthy volunteers more than 50 y old.

CONCLUSION

Patients with CAD show an attenuated MBF increase during mental stress. Their abnormal vasomotor response may contribute to the previously reported induction of ischemic events from mental stress in daily life.

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