Regulation of myocardial blood flow response to mental stress in healthy individuals

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Regulation of myocardial blood flow response to mental stress in healthy individuals and patients with coronary artery disease (CAD) (2, 24, 37, 44). In patients with CAD, mental stress can induce myocardial ischemia (37), and abnormal responses to mental stress are associated with increased rates of daily life ischemic events (21). Even in asymptomatic individuals without clinically overt CAD, an altered blood pressure response to mental stress is associated with electrocardiographic abnormalities and scintigraphic perfusion defects on exercise testing (24).

More recently, mental stress testing has been proposed as a noninvasive means to assess coronary vasomotion and endothelial function (44), because the vasomotor response to mental stress is correlated with that to ACh (6, 13, 44).

Invasive studies have suggested that aging and gender might affect coronary vasomotion and might, therefore, alter the normal, physiological myocardial blood flow response to mental stress. Furthermore, the myocardial blood flow response to any stress depends on the magnitude of stress-induced changes in cardiac work (9, 26). Therefore, before mental stress testing is used in patients for assessing coronary vasomotion, the determinants of the physiological myocardial blood flow response to mental stress need to be evaluated.

Previous noninvasive studies in healthy individuals evaluated changes in left ventricular function (2) or used semiquantitative modalities for evaluating myocardial perfusion during mental stress (19). Invasive techniques, such as intracoronary Doppler-flow velocity measurements, were required to derive quantitative estimates of coronary flow. This technique quantifies coronary flow velocity rather than myocardial blood flow and cannot be applied to determine the flow response to mental stress in larger cohorts of healthy individuals. Thus, to date, the physiological myocardial blood flow response to mental stress has not been quantified.

This limitation has been overcome with the advent of positron emission tomography (PET), which allows the noninvasive quantification of myocardial blood flow. Therefore, the aim of the current study was to determine the physiological myocardial blood flow response to mental stress in healthy individuals using N-13 ammonia PET.

METHODS

Study population. The study population consisted of 24 healthy volunteers (12 males, 12 females, mean age: 49 ± 13 yr, range 31–74 yr) with a low likelihood for CAD. All had a normal resting electrocardiogram (ECG). None of the participants had a history of chest pain or cardiovascular risk factors (12). All participants were nonsmokers, and none had familial hyperlipidemia or diabetes mellitus. All participants over 50 yr had a normal treadmill exercise test. Each participant was admitted to the laboratory after an overnight fast (i.e., at least 10 h after the last meal) with electrocardiographic baseline measurements.
subtracting 7 from 6,828 during the first minute the problem was modified and increased in constraints in a progressively challenging sequence. Every second, two-digit number from a four-digit number under time constraints, investigators asked the participant to subtract a one- or two-digit number from a four-digit number under time constraints in a progressively challenging sequence. Every second the problem was modified and increased in difficulty (e.g., subtracting 3 from 2,904 during the first 2 min, subtracting 7 from 6,828 during minutes 3 and 4, etc.). After an initial increase in heart rate and blood pressure, a stable plateau in hemodynamic response was observed in all participants at minute 2 or 3 of the mental stress protocol. Therefore, a second dose of N-13 ammonia (555–740 MBq) was injected at minute 3 and the mental stress protocol continued for another 4–5 min, i.e., for a total of 7 min. Images were recorded in the same dynamic sequence. Heart rate, arterial blood pressure (automated blood pressure cuff), and a 12-lead ECG were recorded at 1-min intervals throughout the study. The ECG was recorded continuously during the first 2 min of the resting study and throughout the entire stress test. Hemodynamic measurements obtained during the first 2 min after tracer injection were averaged to obtain the rate-pressure product (RPP) as an index of cardiac work (23).

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 at the time of the arithmetic calculation to evaluate the neurohumoral response to mental stress.

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 and absence of perfusion defects. The short-axis images were then displayed as polar maps of the relative myocardial N-13 ammonia distribution at rest and during mental stress. Normal resting perfusion was defined as an N-13 ammonia uptake within 2 standard deviations (SD) of the mean of a normal database previously established at our institution (34).

Quantification of myocardial blood flow. Regional myocardial blood flow at rest and during mental stress was quantified in the vascular territories of the left anterior descending artery (LAD), left circumflex artery, and right coronary artery. Sectorial regions (70–90°) of interest were placed in one basal, one midventricular, and one apical short-axis slice of the left ventricle (9). A small region of interest (25 mm²) was centered in the left ventricular blood pool to derive the arterial input function (9). Myocardial and blood pool 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 these three short-axis images. Because no differences in regional myocardial blood flow were observed, the three territorial blood flow values were averaged, and a single value for myocardial blood flow was obtained in each participant. Partial volume effects were corrected using a recovery coefficient of 0.73, which assumes a uniform left ventricular wall thickness of 1 cm (9). Both the blood pool and myocardial time-activity curves were corrected for physical decay of N-13 ammonia and were fitted using a previously validated two-compartment tracer kinetic model, which corrects for activity spillover from blood pool into the left ventricular myocardium (25). Measurements of myocardial blood flow were derived from the data sets acquired over the first 2 min of the dynamic imaging sequence (25).

Serum lipid and catecholamine measurements. Total serum cholesterol and high-density lipoprotein (HDL) cholesterol were measured using standard enzymatic methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (17). Total cholesterol levels <200 mg/dl were considered normal, cholesterol levels between 200 and 239 mg/dl were considered borderline, and cholesterol levels ≥240 mg/dl were considered elevated. HDL cholesterol ≥35 mg/dl was defined as normal. LDL cholesterol levels <130 mg/dl were considered normal, values between 130 and 159 were considered borderline, and values ≥160 mg/dl were considered as elevated (1). Serum epinephrine and norepinephrine were measured using HPLC.

Statistical analysis. Data are presented as means ± SD. Data are presented for the whole study population, as well as for males and females and three (arbitrarily chosen) age groups: younger than 40 yr of age (n = 9), age 41–60 yr (n = 9), and older than 60 yr (n = 6). Comparisons within groups (age and gender) were performed using Student’s t-test for paired data; comparisons between groups employed ANOVA with Fisher’s protected least significant differences test and Scheffe’s posttest. Correlations were sought using least-squares regression analysis. Possible differences between groups in the magnitude of blood flow and hemodynamic response to mental stress were evaluated by nonparametric Mann-Whitney U-test.

Stepwise logistic regression analysis was then performed to assess relationships between myocardial blood flow (absolute values and blood flow normalized to the RPP; measurements at rest, during mental stress, and stress-induced changes) and epidemiological, serum lipid, and hemodynamic parameters (29). This analysis revealed that the mental stress-induced increase in RPP was the variable that best predicted the magnitude of blood flow increase. A stepwise multiple-regression analysis and all possible subset multiplet-regression analyses were then used to further evaluate the relationship between mental stress-induced blood flow increase and independent variables such as age, gender, total cholesterol, HDL, and LDL, as well as ratios of total cholesterol to LDL cholesterol and HDL cholesterol to LDL cholesterol in all 24 participants. P < 0.05 was considered statistically significant.
Table 1. Hemodynamic parameters

<table>
<thead>
<tr>
<th></th>
<th>&lt;40 yr</th>
<th>40–60 yr</th>
<th>&gt;60 yr</th>
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<th>Females</th>
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<tr>
<td>n</td>
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<td>9</td>
<td>6</td>
<td>12</td>
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<td>50±4</td>
<td>65±9</td>
<td>47±14</td>
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<tr>
<td>Rest</td>
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<td>Mental stress</td>
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<td>Systolic BP, mmHg</td>
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<td>Rest</td>
<td>120±24</td>
<td>117±11</td>
<td>133±22†</td>
<td>131±19</td>
<td>116±21</td>
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<td>133±24*</td>
<td>155±24*</td>
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<tr>
<td>Rest</td>
<td>7,028±2,100</td>
<td>8,422±1,290</td>
<td>8,866±1,700</td>
<td>8,190±1,830</td>
<td>7,858±1,990</td>
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<tr>
<td>Mental stress</td>
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<td>10,675±2,192*</td>
<td>11,605±3,001*</td>
<td>10,637±2,434*</td>
<td>10,229±3,011*</td>
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</table>

Values are means ± SD, n is no. of subjects. BP, Blood pressure. *P < 0.01 vs. measurements at rest, †P < 0.05 vs. 40–60 yr, ‡P < 0.01 vs. under 40 yr.

RESULTS

Hemodynamic findings. Hemodynamic data for the three different age groups and for males and females are shown in Table 1. For the whole study population resting heart rate and RPP increased with age (linear regression: r = 0.56, P = 0.006 for heart rate and r = 0.62, P = 0.002 for RPP, respectively). Mental stress induced significant (P < 0.001) increases in heart rate, systolic blood pressure, and RPP. The magnitude of mental stress-induced changes in heart rate, blood pressure, and RPP was similar between males and females and between the age groups (Fig. 1).

Serum catecholamines and cholesterol levels. Mental stress induced a significant increase in both epinephrine and norepinephrine levels from 26 ± 16 to 42 ± 17 pg/ml (P = 0.01) and from 272 ± 139 to 322 ± 136 pg/ml (P < 0.001), respectively.

The total cholesterol values were below 200 mg/dl (range 160–199 mg/dl) in 17 individuals and between 200 and 239 mg/dl in the remaining 7 participants; for the whole study group the values averaged 194 ± 23 mg/dl. Subfractions of LDL and HDL cholesterol were 120 ± 24 and 46 ± 11 mg/dl, respectively. The calculated LDL-to-HDL ratio was 2.64 ± 1.03. Triglycerides averaged 140 ± 81 mg/dl.

Semi-quantitative analysis (PET polar map analysis). A total of 72 vascular territories (LAD, left circumflex artery, and right coronary artery in the 24 participants) were analyzed. All territories exhibited normal and homogenous tracer uptake on visual and polar map analysis at rest and during mental stress.

Quantitative analysis of myocardial blood flow at rest and during mental stress. At rest myocardial blood flow averaged 0.70 ± 0.14 ml·min⁻¹·g⁻¹ and was similar in the three coronary vascular territories of the LAD (0.67 ± 0.14 ml·min⁻¹·g⁻¹), left circumflex artery (0.76 ± 0.16 ml·min⁻¹·g⁻¹), and right coronary artery (0.67 ± 0.13 ml·min⁻¹·g⁻¹). Mean resting blood flow did not differ between males and females [0.68 ± 0.13 and 0.72 ± 0.14 ml·min⁻¹·g⁻¹, P = not significant (NS)] or between the three age groups (0.62 ± 15, 0.72 ± 13, and 0.67 ± 0.10 ml·min⁻¹·g⁻¹ for individuals younger than 40 yr, 40–60 yr, and older than 60 yr, respectively).

As shown in Fig. 1, mental stress induced a significant increase in mean blood flow (P < 0.001) by ~30% to 0.92 ± 0.21 ml·min⁻¹·g⁻¹ (LAD 0.91 ± 0.21, left circumflex artery 0.98 ± 0.24, right coronary artery 0.95 ± 0.24, and posterior 0.93 ± 0.23).

![Fig. 1. Magnitude of changes in heart rate (HR), systolic blood pressure (SBP), rate-pressure product (RPP), and myocardial blood flow (MBF)](http://ajpheart.physiology.org/Downloadedfromhttp://ajpheart.physiology.org) by 10.220.33.5 on September 9, 2017
0.85 ± 0.19 ml·min⁻¹·g⁻¹). This increase in blood flow was unrelated to age or gender (Fig. 1). Myocardial blood flow and RPP were significantly correlated at rest (r = 0.72, P = 0.001) and during mental stress (r = 0.83, P = 0.0001; Fig. 2). Furthermore, mental stress-induced increases in the RPP were associated with proportional increases in myocardial blood flow (Fig. 2).

Coronary vascular resistance. The coronary vascular resistance was calculated as the ratio of mean arterial blood pressure over mean myocardial blood flow (27). At rest the resistance was 132 ± 32 mmHg·ml⁻¹·min⁻¹·g, and during mental stress it declined to 112 ± 16 mmHg·ml⁻¹·min⁻¹·g (P = 0.001). The magnitude of mental stress-induced decline in resistance (−14%) was independent of age and gender (resistance declined by 15 ± 12% in individuals <40 yr, by 12 ± 6% in individuals 40–60 yr, by 18 ± 9% in individuals >60 yr, by 14 ± 12% in males, and by 13 ± 6% in females; P = NS by ANOVA between subgroups).

Multivariate analysis. Multiple-regression analysis revealed that the degree of increase in cardiac work (the RPP) was the best predictor of the magnitude in myocardial blood flow changes: y = 5.71 × 10⁻³ × change in RPP + 0.081; r = 0.72, F = 15.6, P = 0.001. Further stepwise multiple-regression analysis including all 24 participants revealed none of the other variables as significant and independent predictors of the myocardial blood flow response to mental stress [age: F = 1.1, P = 0.31 (Fig. 3); gender: F = 1.11, P = 0.3; resting RPP: F = 0.37, P = 0.82; total cholesterol: F = 1.13, P = 0.29; HDL: F = 0.52, P = 0.48; LDL: F = 0.23, P = 0.64; total cholesterol to HDL cholesterol: F = 0.01, P = 0.92; HDL cholesterol to LDL cholesterol: F = 0.14, P = 0.71].

DISCUSSION

Mental stress testing has been proposed as a noninvasive tool to evaluate endothelium-dependent coronary vasomotion (44). The current study in healthy individuals quantified the physiological myocardial blood flow response to mental stress and revealed that the magnitude of the blood flow response to mental stress was solely determined by the magnitude of stress-induced changes in cardiac work. The proportional relationship between these two parameters is in concordance with the concept that under physiological conditions myocardial blood flow and left ventricular oxygen consumption are closely coupled (9, 26). Because neither age, gender, nor serum lipid levels affected the myocardial blood flow response, mental stress testing might be useful to probe coronary vasomotion noninvasively.

Regression of coronary flow during mental stress. Sympathetic stimuli such as mental stress induce the release of catecholamines from the adrenal medulla and cardiac nerve terminals (14) leading to moderate increases in heart rate, arterial blood pressure, and myocardial oxygen demand. This response is comparable to low-level exercise. The regulation of coronary flow during mental stress involves activation of β₁-receptors (indirect vasodilatation via increased metabolism), vascular smooth muscle α₁- (vasoconstriction) and β₂- (vasodilatation) receptors, and activation of endothelial α₂-receptors [release of endothelium-derived relaxing factor-nitric oxide (EDRF-NO)] (11). Shear stress due to increased coronary flow causes further release of vasoactive substances, in particular NO (6, 13, 44).

![Fig. 2. Correlation between cardiac work (the RPP) and MBF. Both parameters were significantly correlated at rest (A) and during mental stress (B). Stress-induced changes in MBF were also significantly related to changes in cardiac work (C). BPM, beats/min; n, no. of subjects.](http://ajpheart.physiology.org/)

![Fig. 3. Lack of correlation between age and stress-induced changes in MBF.](http://ajpheart.physiology.org/)
The coronary vasomotor response to mental stress is correlated with that to ACh as a test of endothelial function: Yeung et al. (44) employed mental stress testing in patients with CAD and found a significant correlation between the (epicardial) coronary vasomotor response to ACh and mental stress. In two other studies, the mental stress-induced increase in forearm blood flow was blunted after intra-arterial administration of the NO synthase inhibitor N^G^-monomethyl-L-arginine (6, 13). These observations suggest that normal endothelium limits the vasoconstrictor effects of catecholamines (40, 41), whereas arteries with dysfunctional endothelium exhibit a markedly increased vasconstrictor response to catecholamines (30). Mental stress also affects the vasomotion of coronary resistance vessels, and the physiological response is characterized by an increase in blood flow (10). In contrast, CAD patients exhibit a markedly attenuated blood flow increase in response to mental stress which can, however, be augmented by intracoronary infusion of the α-receptor blocker phentolamine (10).

Collectively, these data imply an unopposed and increased adrenergic vasoconstrictor tone once the functional integrity of the coronary endothelium is altered. By contrast, in healthy individuals the endothelial release of NO (40, 41) and other vasoactive substances opposes the mental stress-induced α-adrenergic coronary vasoconstriction, resulting in a net increase in coronary blood flow (10). Consistently, the present study revealed a significant increase in myocardial blood flow in response to mental stress in healthy individuals.

Effects of age and gender on the myocardial blood flow response to mental stress. The degree to which myocardial blood flow changes during sympathetic stimulation might be affected by age, gender, or serum lipid levels (7, 15, 45). Previous studies that used intracoronary ACh and Doppler-flow measurements indicated that aging (independent of other risk factors) alters endothelium-dependent coronary vasomotion (7, 15, 45). Zeiher et al. (45) reported a strong negative correlation between age and the coronary flow response to ACh. In patients with a normal exercise test, angiographically normal coronary arteries, and in the absence of coronary risk factors, Egashira et al. (15) and Chauhan et al. (7) also found a significant negative correlation between the peak coronary flow response to ACh and age, whereas the endothelial-independent vasomotor response to papaverine (7, 15) and nitroglycerin (7) was independent of age. Therefore, if mental stress testing was indeed a specific test of endothelium-dependent coronary vasomotion (6, 13, 44), an age-dependent attenuation of the myocardial blood flow response to it would have been expected. However, no such effect was observed.

How can these discrepancies be reconciled? First, although the vasomotor and blood flow responses to mental stress and to intracoronary ACh are correlated, they may involve different pathophysiological mechanisms. Although ACh causes direct release of NO through its endothelial receptors (18), the blood flow response to mental stress depends not only on endothelial function but also on other factors, such as the serum catecholamine levels, stress-induced changes in cardiac work, and the local release of vasoactive mediators. For instance, increases in cardiac work during sympathetic stimulation may be accompanied by increased levels of circulating adenosine, which are closely related to the magnitude and time of work-induced hyperemia (28). Thus, although the vasomotor response to mental stress is largely governed by endothelium-dependent mechanisms, our data suggest that the myocardial blood flow response to mental stress does not selectively probe coronary endothelial function but might rather provide an index of overall coronary vasomotor function.

Second, the effects of intracoronary ACh are dose dependent and show considerable individual variations. In healthy individuals the maximal flow increases in response to intracoronary ACh varied between 125 and 660% of baseline (7, 15). In contrast, mental stress in the present study induced an increase in blood flow to only 130% of baseline (range 114–200%), which is comparable to other sympathetic stimuli, such as cold pressor testing (4, 32). Given this considerably smaller blood flow response, small age-related differences in stress-induced changes in myocardial blood flow are unlikely to be detected.

Third, aging is associated with a number of physiological alterations, such as an elevated systolic blood pressure and myocardial blood flow at rest (8, 9) and an attenuated increase in left ventricular ejection fraction during exercise (35). However, many of these age-related physiological changes can be modified by physical training and exercise (16, 33). In addition, chronic exercise can increase coronary endothelial NO production (38). In regard to the present study population, a selection bias toward healthier subjects cannot be excluded. None of the study participants were smokers or obese, and none had arterial hypertension or hypercholesterolemia. This suggests a healthier lifestyle because regular physical activity and presence of cardiovascular risk factors are inversely related (20, 36).

Middle-aged men exhibit a greater prevalence and severity of coronary atherosclerosis (42), but the reported effects of gender on coronary vasomotor function have been controversial (7, 45). In particular, there is no evidence that male gender (in the absence of established coronary risk factors) is associated with abnormalities in endothelium-dependent coronary vasomotion (7, 45). Consistently, the magnitude of blood flow increase during mental stress was independent of gender in the current study.

Study limitations. With a single blood sample (as opposed to serial blood sampling) during mental stress, the individual peak response in serum catecholamines might have been missed in our study. Moreover, venous forearm blood sampling, in particular a single blood sample, may be inadequate to assess accurately stress-related individual changes in serum catecholamines (3). However, the current stress-induced changes in
serum norepinephrine and epinephrine levels prove that the test was effective.

The individual response to sympathetic stimuli may vary (for instance depending on the motivation during mental stress). However, the 30% increase in RPP observed is similar to that reported in previous studies employing mental stress (2, 44) or other sympathetic stimuli (4, 32).

It would be nice to have reproducibility data for use as a database for future studies, however, this is not provided in this paper. However, a good reproducibility of mental arithmetic testing has been shown previously (5, 22). For instance, Jern et al. (22) employed the same mental stress protocol as the present study and reported a high test-retest correlation for the stress-induced changes in heart rate and systolic and diastolic blood pressure response (r = 0.81, 0.76 and 0.92, respectively, all P < 0.01). The reproducibility of myocardial blood flow measurements with PET has also been shown previously. Nagamachi et al. (31) reported an excellent correlation between quantitative blood flow measurements performed on two different days (r = 0.63, P < 0.005). No data are currently available regarding the intraindividual reproducibility of measurements of myocardial blood flow during mental stress. However, our study demonstrated a strong correlation between the hemodynamic response to mental stress and changes in myocardial blood flow (Fig. 2); and in the multiple-regression analysis, changes in blood flow were solely determined by the magnitude of increase in cardiac work. This follows several previous studies from this and other groups which demonstrated that the rate pressure product as an index of cardiac blood flow should be the most important determinant of myocardial blood flow. Thus it should be noted that increases in myocardial blood flow can only be expected when mental stress testing indeed induces an increase in cardiac work.

Only six participants were older than 60 yr, and only two of these were older than 70 yr. Thus the effect of mental stress on myocardial blood flow in septuagenarians was not addressed in this study.

All participants had a low pretest probability for CAD of <5% based on the criteria established by Diamond and Forrester (12). In addition, normal treadmill ECGs were required in all subjects older than 50 yr. However, early stages of CAD could have been ruled out with certainty only by an intravascular ultrasound. Such an invasive study was considered ethically unacceptable.

In healthy individuals, the myocardial blood flow response to mental stress is independent of age, gender, or serum lipid levels and is only determined by the magnitude of stress-induced increases in cardiac work. Because the coronary vasomotor response to mental stress and ACh are closely correlated, mental stress testing has been proposed previously as a means to assess coronary endothelial function. The lack of any effect of aging on myocardial blood flow in the present study suggests that mental stress may not selectively test endothelial function but rather provide an index of overall coronary vasomotor function.

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REFERENCES


