

Comparison of Peripheral Arterial Response to Mental Stress in Men Versus Women With Coronary Artery Disease

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There are profound gender-related differences in the incidence, presentation, and outcomes of coronary artery disease (CAD). These differences are not entirely explained by traditional cardiovascular risk factors. Nontraditional risk factors, such as psychological traits, have increasingly been recognized as important contributors to the genesis and outcomes of CAD. Mental stress induces significant peripheral arterial vasoconstriction, with consequent increases in heart rate and blood pressure. These changes are thought to underlie the development of myocardial ischemia and other mental stress-induced adverse cardiac events in patients with CAD. This study examined for gender-related differences in peripheral arterial response to mental stress in a cohort of patients with CAD using a novel peripheral arterial tonometric (PAT) technique. There were 211 patients (77 women; 37%) with a documented history of CAD and a mean age of 64 ± 9 years. Patients were enrolled from August 18, 2004, to February 21, 2007. Mental stress was induced using a public speaking task. Hemodynamic and PAT measurements were recorded during rest and mental stress. The PAT response was calculated as a ratio of pulse wave amplitude during stress to at rest. PAT responses were compared between men and women. The PAT ratio (during stress to at rest) was significantly higher in women compared with men. Mean PAT ratio was 0.80 ± 0.72 in women compared with 0.59 ± 0.48 in men ($p = 0.032$). This finding remained significant after controlling for possible confounding factors ($p = 0.037$). In conclusion, peripheral vasoconstrictive response to mental stress was more pronounced in men compared with women. This finding may suggest that men have higher susceptibility to mental stress-related adverse effects. Additional studies are needed to determine the significance of this finding. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102:970–974)

Little has been reported regarding gender-related differences in mental stress-induced vascular reactivity. However, there is consistent evidence that women have decreased sensitivity to the vasoconstrictor effects of norepinephrine.^{1–6} Women have also been shown to have higher basal nitric oxide compared with men.^{7,8} Collectively, these observations suggest that men may have more intense vascular reactivity to mental stress compared with women. In patients with coronary artery disease (CAD), these changes may increase vulnerability to mental stress-induced myocardial ischemia and other mental stress-related adverse events.^{9–12} In this study, we sought to ex-

amine for gender-related differences in peripheral arterial response to mental stress in a cohort of patients with CAD using a novel noninvasive peripheral arterial tonometric (PAT) technique.

Methods

Subjects in this study were recruited from outpatient clinics affiliated with university-based medical centers. Eligibility criteria included age >18 years and a documented clinical diagnosis of CAD supported by (1) angiographic evidence of >50% stenosis in ≥ 1 coronary artery or previous percutaneous intervention or coronary artery bypass graft surgery; (2) previous myocardial infarction (MI) documented with increased troponin in the range typical of MI, Q-wave abnormalities on electrocardiogram, or fixed perfusion abnormalities on nuclear scan; or (3) a positive radionuclide pharmacologic or exercise stress test result. Patients were excluded if they had unstable angina or acute MI within the 2 months preceding enrollment, a severe co-morbid medical problem restricting life-expectancy to <5 years, pregnancy, or body weight >400 lbs.

Study procedures were performed the morning after an overnight fast. Beta blockers, calcium channel blockers, and long-acting nitrates were withheld the night before testing. Demographic and psychosocial characteristics were obtained before study procedures. Patients were initially rested for 30 minutes in a temperature-controlled (21°C to 23°C)

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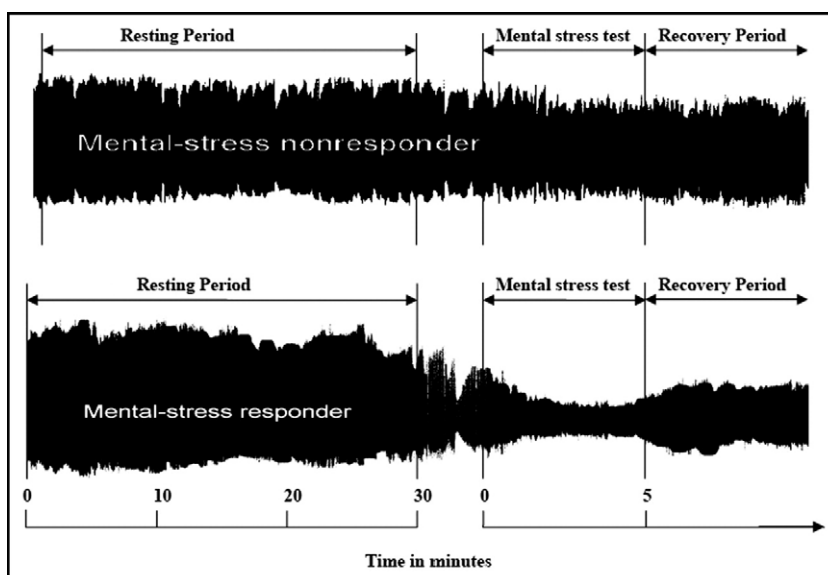


Figure 1. Representative examples of PAT tracing. (Top tracing) A patient with no significant response to mental stress; (bottom tracing), significant peripheral arterial vasoconstrictive response to mental stress. The PAT response was calculated as a ratio of pulse wave amplitude during stress and at rest.

Table 1
Demographic and clinical characteristics of the study population

Variable	Men (n = 134)	Women (n = 77)	p Value
Mean age (yrs)	64 ± 9	64 ± 9	NS
Ethnicity			
Caucasian	118 (89%)	68 (91%)	NS
African American	6 (5%)	7 (9%)	NS
No. of diseased coronary vessels*	2.2 ± 0.82	1.9 ± 0.93	0.034
Previous MI	26 (19%)	13 (17%)	NS
Previous percutaneous coronary intervention	59 (44%)	32 (42%)	NS
History of exercise or adenosine-induced myocardial ischemia	43 (32%)	31 (40%)	NS
Smoking status:			
Never	23 (17%)	40 (52%)	<0.001
Current	22 (17%)	8 (10%)	
Former	89 (66%)	29 (38%)	
Hypertension	104 (78%)	63 (82%)	NS
Diabetes mellitus	48 (46%)	20 (26%)	NS
Angina pectoris	83 (62%)	54 (70%)	NS
Hyperlipidemia	122 (91%)	68 (88%)	NS
β Blockers	111 (82%)	49 (64%)	0.002
Angiotensin-converting enzyme inhibitors	79 (59%)	31 (40%)	0.009
Calcium channel blockers	21 (16%)	24 (31%)	0.008
Hormone replacement therapy		5 (6.5%)	
Body mass index (kg/m ²)	30 ± 4	30 ± 7	NS

Baseline demographic and clinical characteristics in men and women.

Values expressed as mean ± SD or number (percent).

* This information available for only 143 patients (97 men, 46 women).

dark and quiet room. Heart rate (HR) and blood pressure (BP) were measured every 5 minutes using an electrocardiograph monitor and automatic oscillometric device (Dinamap; Critikon Inc., Tampa, Florida), respectively. Mental stress was then induced through a public speaking task performed in front of a small white-coated audience, as in previous research.¹³ Subjects were given a scenario describing a real-life stressful event and asked to make up a realistic story around it. Subjects were given 2 minutes to

prepare their speech and 3 minutes to speak. They were told that their speech would be videotaped and the laboratory staff would replay the tape to rate it for content, quality, and duration of the speech. Hemodynamic measurements were obtained every minute during the preparation and speech periods and at 1, 3, 5, and 10 minutes into the recovery period. Systolic BP and HR were used to calculate the double product value (double product = systolic BP × HR).

Table 2
Mental stress–induced hemodynamic and peripheral arterial tonometric (PAT) responses in men and women

	Men (n = 134)	Women (n = 77)	p Value
Hemodynamic responses			
Increase in systolic BP (mm Hg)	44 ± 20	43 ± 20	0.89
Increase in diastolic BP (mm Hg)	28 ± 11	29 ± 12	0.53
Increase in HR (beats/min)	19 ± 12	22 ± 14	0.11
Increase in double product	5,682 ± 2,965	6,353 ± 3,308	0.13
PAT response			
Unadjusted	0.59 ± 0.48	0.80 ± 0.72	0.032
Adjusted*	0.48 (0.38–0.48)	0.61 (0.38–0.58)	0.037

Values expressed as mean ± SD or mean (95% confidence interval).

*Controlling for co-morbid conditions (diabetes, hypertension, and smoking status), body mass index, and medication status (β blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors).

The PAT device (Itamar-Medical, Caesarea, Israel) was used to continuously measure pulse wave amplitude in the finger during rest and mental stress, as in previous research.¹⁴ It applied a constant pressure of 40 to 70 mm Hg to eliminate venous stasis and unload arterial wall tension within the probed part of the finger. The device was connected through thin flexible tubing to an isolated volume reservoir to buffer pressure changes within the probe. Another volume reservoir not connected to the probe served as a pressure reference. The distal compartment of the device was connected to a pressure transducer that sensed pulsatile fluctuations exerted by blood volume changes in the digital arteries. In this study, the device was applied to the index finger. Attention was paid not to use the same extremity for BP measurements. PAT measurements were recorded during rest and mental stress (2-minute speech preparation and 3-minute speaking task). Pressure changes were fed to a personal computer, where the signal was filtered (0.3 to 30 Hz), amplified, stored, and analyzed in an operator-independent manner. Noise was removed from the tracing using electronic filtering. Baseline pulse wave amplitude was determined by averaging during the entire rest period. Stress amplitude was determined by averaging during the 5-minute stress period. Using these measurements, the PAT response was calculated as a ratio of the pulse wave amplitude during stress to at rest. Representative PAT signals and the time course of the study were shown in Figure 1.

Results were expressed as mean ± SD for continuous variables and frequency and percentage for categorical variables. Stress hemodynamic responses were calculated as the difference between measurements during stress and at rest. Statistical significance was considered at $p < 0.05$. Univariable and multivariable analyses were used to examine the influence of gender on PAT response. In addition to gender, the latter analysis included as covariates co-morbid conditions (diabetes, hypertension, and smoking status), medication status (β blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors), and body mass index. Log transformation of the PAT ratio was conducted

to satisfy the Gaussian distribution assumption of the model. All analyses were performed using SAS statistical software (SAS Inc., Cary, North Carolina).

Results

A total of 211 patients were studied; 134 men (63%) and 77 women (37%). Baseline demographics by gender groups are listed in Table 1.

Mental stress induced significant changes in systolic BP, diastolic BP, HR, and double product compared with the condition at rest in the study population combining both men and women ($p < 0.001$). Comparing hemodynamic responses with mental stress across gender groups did not show differences in systolic BP, diastolic BP, HR, or double product between men and women ($p = 0.89$, $p = 0.53$, $p = 0.11$, and $p = 0.13$, respectively). Hemodynamic responses to mental stress by gender groups are listed in Table 2.

Most patients (180 [85%]) developed a vasoconstrictive PAT response to mental stress (PAT ratio < 1), and 31 patients (15%) developed a vasodilative response (PAT ratio > 1). The rate of vasoconstrictive response was significantly higher in men compared with women (91% vs 75%; $p = 0.002$).

We observed a significantly higher PAT ratio in women compared with men. Mean PAT ratio was 0.80 ± 0.72 in women compared with 0.59 ± 0.48 in men ($p = 0.032$). Using multivariable analysis to control for possible confounding factors (see statistical section), this gender effect remained significant, with women having higher PAT ratios than men ($p = 0.037$). The adjusted mean PAT ratio in women was 0.61 (95% confidence interval 0.43 to 0.79) compared with 0.48 (95% confidence interval 0.38 to 0.58) in men (Table 2). These findings suggest that men showed a more pronounced vasoconstrictive response during mental stress compared with women.

Discussion

In this study, we examined for gender-related differences in peripheral arterial response to mental stress. Our findings indicated that men showed a more pronounced peripheral vasoconstrictive response to mental stress compared with women. The average PAT ratio (during stress to at rest) was 0.59 in men compared with 0.80 in women. These findings were consistent with previous reports suggesting that women had decreased sensitivity to the vasoconstrictor effects of norepinephrine, as well as higher basal nitric oxide.^{1–8}

We explored the relation between gender and vascular reactivity to mental stress in an effort to unravel mechanisms that might explain the observed gender-related differences in prevalence, clinical presentation, and outcomes of CAD. Mental stress has been shown to induce transient myocardial ischemia and other adverse cardiac events in patients with CAD. Peripheral arterial vasoconstriction has consistently been reported as an underlying mechanism for ischemia development in this setting. Laboratory-induced mental stress is a direct simulation of everyday life stress.^{15–19} Thus, it is possible that the vascular responses to mental stress observed in this study could represent frequent daily life occurrences. There is also evidence that situational

stressors similar to the 1 used in this study could lead to transient endothelial dysfunction lasting up to 4 hours.²⁰ Potentially, these observations could provide a mechanistic link between mental stress and myocardial ischemia and other cardiac events. That men had a more vasoconstrictive response to mental stress may imply higher susceptibility to mental stress-related adverse events. This needs to be validated in a follow-up study.

Arguably, many factors might be operative in explaining the gender differences observed in this study. We believe the findings we observed were caused by true physiologic differences between men and women. Estrogen is a known vasodilator and mediates this effect in part by stimulating the release of nitric oxide and prostacyclin from the vessel wall.^{21–23} It is intriguing that we found remarkable differences in this study, although most of our women participants were postmenopausal. Another unique and relevant correlate is the existence of some reports suggesting that women have better coping skills with situational stressors than men.^{24–26} This could potentially attenuate their physiologic adrenergic response to psychological stress.

We did not find significant differences in BP or HR responses to mental stress between men and women. Similar findings have been reported in other studies.²⁷ Furthermore; we also found that differences in the mental stress PAT response between men and women did not translate into differences in HR or BP responses. This is not surprising because peripheral arterial tonometry does not measure pressure; instead, it measures peripheral blood volume. Hence, changes in peripheral blood volume may not necessarily reflect changes in BP. Another potential reason for this discrepancy was the BP measurement techniques used in this study. Using the traditional sphygmomanometric brachial BP technique may miss rapid changes that would be captured only by beat-by-beat measurements. Another potential explanation is that in our cohort, men were more likely to be tested under the effects of β blockers or calcium channel blockers (Table 1), which might have blunted their BP or HR response to mental stress.

The gender groups in our study were not prospectively matched in terms of their CAD severity and other co-morbid conditions. The men in this cohort tended to have more severe CAD compared with women. This is probably related to the similar mean age for men and women in this study. Typically, age-matched women are expected to have less severe atherosclerotic CAD compared with their male counterparts.^{28,29} However, in our analysis, differences in PAT measurements between men and women remained significant after statistically controlling for CAD severity factors and other co-morbid medical conditions.

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