

EDITORIAL COMMENT

# Sex Differences in Mental Stress-Induced Myocardial Ischemia



## Are Women From Venus?\*

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Psychological or mental stress, a common complaint in cardiac patients, results in a cascade of responses that are triggered by activation of the hypothalamic-pituitary axis and mediated by the adrenocorticotrophic hormones and concomitant proinflammatory responses. Persistent activation of these pathways adversely affects the cardiovascular system by promoting autonomic imbalances, oxidant and inflammatory signaling, as well as dysglycemia, atherogenic dyslipidemia, and vascular dysfunction. Importantly, behavioral sequelae of unopposed exposure to mental stress such as psychomotor retardation, anhedonia, and lack of motivation may result in profound physical inactivity and medical noncompliance that further increase cardiovascular risk.

The acute effects of psychosocial stress are often evaluated by performance of a mentally challenging task that attempts to mimic daily life stressors such as public speaking and mental arithmetic tasks. Mental stress elicits cardiovascular responses that are distinctly different from those induced by physical exertion, exemplified by vasoconstriction in both the coronary and peripheral circulation in the presence of atherosclerotic disease (1). Compared with the dramatic hemodynamic changes associated with physical exercise, mental stress provocation is accompanied by a far more attenuated blood

pressure and heart rate increase, but can, nonetheless, occasionally precipitate myocardial ischemia because of concomitant vasoconstriction. Unlike diagnostic exercise testing, mental stress-induced myocardial ischemia (MSIMI) is rarely associated with abnormal electrocardiographic changes or anginal chest pain, and is often diagnosed using echocardiographic testing for wall motion abnormalities and/or scintigraphic defects (2).

The prevalence of MSIMI in stable CAD varies widely ( $\approx 20\%$  to  $70\%$ ) in published reports, likely the result of differences in the stressors used, diagnostic techniques employed, and psychosocial profiles of study subjects. Irrespective of the provocateur or diagnostic modality used, the presence of MSIMI increases the risk of adverse cardiac events and overall mortality by more than 2-fold (3). MSIMI appears to be amenable to pharmacological and nonpharmacological interventions, and early results indicate that abolishing MSIMI may improve clinical outcomes (4,5). Thus, it is possible that MSIMI identifies a high-risk vulnerable population in which specific treatment may result in improved outcomes, implying that its diagnosis may improve risk stratification and secondary prevention.

In his 1992 book, *Men Are From Mars, Women Are From Venus* (6), author John Gray argues that women and men have such fundamental psychological differences in their responses to mental stress that they can be thought of as though they came from different planets. Is this metaphor of women and men coming from different planets in their responses to mental stress applicable to physiological responses that may result in MSIMI? The article by Samad et al. (7) in this issue of the *Journal* addresses sex differences in cardiovascular, psychological, and rheological effects of mental stress. Screening for

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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MSIMI in stable coronary artery disease (CAD) patients enrolled in the REMIT trial was performed using echocardiography, and MSIMI was diagnosed either as worsening of wall motion abnormalities or as a drop in left ventricular ejection fraction during at least 1 of 3 mental stress tasks (4).

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The reported incidence of MSIMI in this study population is far greater than previously reported in patients with CAD. This may be partly because of variations in imaging techniques utilized, stress stimuli employed, and the severity of underlying CAD. In general, techniques using nuclear imaging have reported a lower incidence of perfusion defects with mental stress. It has been suggested that further wall motion abnormalities in those with existing wall motion abnormalities may occur in the absence of true ischemia as a result of changes in afterload. A number of patients in this study had previous myocardial infarction, and afterload changes are significant during mental stress and may at least partly account for the higher incidence of MSIMI observed with echocardiographic testing.

Of the 310 patients in this study, only 18% were women. Of these women, 57% had MSIMI. Even though the blood pressure responses to mental stress were greater in men, a slightly lower proportion of men (42%) had MSIMI. Although these data may be indicative of a true sex-specific difference in MSIMI, some caution is appropriate in this interpretation. First, this is a relatively small sample size of women. Secondly, there are significant sex differences in some important characteristics of the enrolled

subjects that may explain the differences in MSIMI. For example, the prevalence of depressive symptoms, which are established risk factors for MSIMI, was also almost 3-fold higher in women, and adjustment for depressive status indeed abolished the reported sex differences in MSIMI. Similarly, a greater proportion of women than men were African Americans, in whom stress may be more prevalent.

In a subgroup study, increased platelet aggregability in response to collagen was noted after mental stress in women. This needs to be considered in light of higher baseline platelet aggregation in response to other agonists, and the variable and somewhat higher use of aspirin and clopidogrel in women, which complicates interpretation of these findings. Sex-specific studies in subjects free of antiplatelet therapy will be needed to study this phenomenon further. Data on microvascular vasoconstriction and activation of the hypothalamic and adrenergic systems will also be informative to further explore differences in factors precipitating MSIMI. Whether platelet aggregation plays a causative role, or is the result of MSIMI, or is unrelated to MSIMI remains unclear.

The provocative findings of Samad et al. (7) certainly provide impetus for further research in understanding the influence of sex on mental stress-mediated cardiovascular responses including myocardial ischemia and leaves unanswered the question of whether women are really from Venus.

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**KEY WORDS** mental stress, myocardial ischemia, sex differences