Mental Stress and Myocardial Ischemia: Young Women at Risk
Anita Wokhu, MD; Carl J. Pepine, MD

Women with obstructive coronary artery disease (CAD) have poor outcomes relative to otherwise comparable men. More women than men die after a first myocardial infarction.1 Younger women (<55 years) have a particularly unfavorable prognosis after myocardial infarction relative to male counterparts.2 Mechanisms for these differential outcomes are unclear, but since younger women have worse pre-event health status versus men, including lower overall and mental health qualities of life,3 it is likely that the adverse condition begins long before the acute event.

Attention has increasingly focused on psychosocial or mental stressors as potential nontraditional CAD risk conditions. In the Psychophysiological Investigations of Myocardial Ischemia Study, we found that mental stress–induced ischemia predicted increased risk for all-cause mortality in patients with obstructive CAD and exercise-induced ischemia.4 In a cohort of women with symptoms and signs of ischemic heart disease (mean age 58 years) from the Women’s Ischemia Syndrome Evaluation, mostly without obstructive CAD, we found associations between psychosocial factors and premature mortality.5 Over 9.3 years, the Spielberger Trait Anxiety Index and Beck Depression Inventory scores (hazard ratio 1.09, 95% CI 1.02–1.15, and hazard ratio 0.86, CI 0.78–0.93, respectively) and very good self-rated health (versus poor self-rated health, hazard ratio 0.33, CI 0.12–0.96) each independently predicted mortality risk. These results extend prior knowledge in female ischemic heart disease /CAD populations. Clearly, psychosocial factors link with adverse outcomes among women with ischemic heart disease, but how mental stress uniquely modulates the course of younger women remains unclear.

Physiology of Mental Stress in CAD
In CAD patients, mental stress is a well-described provocateur of ischemia. Mental stress increases myocardial oxygen demand. The physiologic response to mental stress encompasses an increased heart rate and often a peripheral vasoconstrictor response that increases left ventricular (LV) afterload. This is in contrast to physical exertion where a vasodilatory response predominates. In health, mental stress may have variable effects on cardiac output and is occasionally associated with a decline in LV ejection fraction.6 In CAD patients, a subset (20% to 70%) demonstrate a pronounced response, termed mental stress–induced myocardial ischemia (MSIMI), defined by left ventricular ejection fraction reduction ≥5%, new or worsening regional wall motion abnormalities, or new myocardial perfusion defects.7

There is interest in MSIMI as a metric that may reveal an individual’s cardiovascular vulnerability to psychosocial or mental stressors. Ambulatory electrocardiographic analysis reveals asymptomatic ischemia in patients with MSIMI. Exercise testing, in contrast, does not appear to differentiate patients who experience ambulatory electrocardiographic abnormalities.8 Additionally, in younger CAD patients, MSIMI is significantly associated with angina frequency.9 MSIMI is associated with a more than doubling of risk for major adverse cardiovascular events, including mortality.4,7

MSIMI in Women
Why women should have a propensity for mental stress ischemia, versus comparable men, is unclear. In this issue, Vaccarino et al10 investigate MSIMI in women with CAD and focus on younger women (<50 years). The prevalence of MSIMI was only about 1 in 6, which is less than previous reports. MSIMI frequency measured using quantitative automated analysis of perfusion defects was greater in women than in men. By visual analysis, which facilitates artifact recognition and may be more representative of clinical practice, sex-related differences in extent of MSIMI were still present.
Identifying an interaction between age and sex, the authors characterized higher levels of MSIMI in the young women. MSIMI occurred in one third of young women and was more frequent versus younger men and older women. Although these data should be approached cautiously because of the small size of the subgroup of young women, it is reassuring to note that a similar tendency was observed in the larger subgroup aged 51 to 60 years. These findings suggest that younger women may have a unique vulnerability to mental stress.

In these patients with MSIMI, it is tempting to simply dismiss the mental stress evaluation as a submaximal version of conventional stress. Ischemia with conventional stress testing was, in fact, more common and more extensive than MSIMI. However, unlike MSIMI, the sex-based differences with exertion were inconsistent when comparing quantitative and visual analysis results. Despite general concordance, ischemia with mental stress can occur independently of ischemia with exercise, and has been reported in 11% to 29% of cohorts. Others suggest that twice as many patients demonstrate MSIMI than with physical stress using echocardiographic criteria. Therefore, MSIMI is likely very different versus exertional ischemia.

These findings add to the limited knowledge on MSIMI in women. York et al reported MSIMI in about one third of patients, with no sex-based differences by visual analysis of nuclear perfusion studies. In contrast, as noted above, MSIMI occurred in over half of women evaluated using mainly echocardiographic criteria and was more frequent in women than men.

**Techniques of MSIMI Assessment**

In addition to unique study populations, differences in MSIMI across these studies may relate, in part, to the ischemia assessment modality. Nuclear perfusion studies yield lower rates of MSIMI than radionuclide or echocardiographic LV function studies. It is relevant to note that in prognostic assessments of MSIMI, functionally defined MSIMI correlates with adverse cardiovascular outcomes. However, when LV dysfunction results from stress, the term MSIMI may overstate the role of ischemia. There may be mechanisms that suppress LV function beyond limitations in myocardial flow. These include those precipitated by dynamic loading, neurohormones, metabolic effects, and inflammatory factors.

**Nonobstructive CAD, the Stress Response, and Microcirculatory Dysfunction in Women**

Recently, there has been considerable interest in the high and increasing prevalence of nonobstructive CAD among women (and men) with symptoms and signs of ischemic heart disease. Within this population, the phenotype characterized by coronary microvascular dysfunction has been associated with increased risk for adverse outcomes. This may also be a substrate for MSIMI as coronary microvascular dilatation is the normal response to mental stress. In contrast, in CAD patients studied during mental tasks, there is paradoxical constriction or failure to dilate in the microcirculation. Positron emission tomography studies also document reduced coronary flow reserve in these patients, which portends worsened cardiovascular outcomes.

The model of mental stress–induced microcirculatory dysfunction in MSIMI fits current understanding of symptomatic nonobstructive CAD in women. In the affected women, many of whom are younger (versus women with obstructive CAD), stress perfusion defects are provoked by pharmacologic vasodilators, even in the absence of flow-limiting epicardial disease. Nonexertional complaints are common. In women with so-called “normal coronary arteries,” abnormal brachial flow–mediated dilatation is 4 times more likely if MSIMI is detected. Clinically, we may be able to identify these women. Inadequate brachial flow–mediated dilatation has been linked to premature onset “hot flashes” in middle-aged women; the premature onset of vasomotor symptoms before menopause seems to identify a subgroup of younger-middle-aged women with higher CAD mortality.

Neurohormonal and hormonal responses to mental stress may further elaborate MSIMI. In addition to acute surges in epinephrine, the heart has its own endocrine functions effecting changes in the microcirculation and endothelial signaling. In addition, the hypothalamic–pituitary–adrenocortical axis is activated. Release of cortisol and corticotropin–releasing hormone has systemic effects on inflammation, microcirculation, blood pressure, and platelet function. This complex combination of events ensures that hormonal milieu in situations of stress is not temporally confined to the actual stress event. Impairments in coronary endothelial function may linger 90 minutes after a mental stress event.

The observation of MSIMI in the stress laboratory likely underestimates mental stress in daily life. Repeated exposures to a mental or psychosocial stressor could potentiate microvascular dysfunction, resulting in a loss of vasoprotection from the endothelium. Situations of chronic mental stress, therefore, may result in chronic subclinical ischemia. Depressed states associated with mental stress also are associated with excess serotonin, a constrictor of coronary microvasculature.

**Controlling Risk in Young Women**

Vaccarino and colleagues focused on young women with CAD who demonstrate a heightened ischemic response to mental
stress stimulus. Why might young women be prone to MSIMI? Sex-specific hormones may be operative, including estrogen, progesterone, or absence of testosterone, and could be differentially modulating perception of stress or cardiovascular vulnerability. The propensity to MSIMI also may be psychosocial in origin, as these factors have been predictive not only of cardiovascular events but also risk factor development in women.²,⁴

Beyond traditional risk factor modification and antianginal therapy, there is no therapeutic silver bullet to treat either MSIMI or coronary microvascular dysfunction. However, identification of MSIMI has potential management implications in high-risk populations, but this requires further study. Treatments such as escitalopram, which impacts platelet aggregability, or stress management techniques have emerged and target pathophysiological changes associated with MSIMI with negligible impact on exercise-induced ischemia.²⁵ Some next steps are to further validate that young woman constitute a population highly vulnerable to mental stress from larger cohort data sets and assess the extent to which they benefit from stress mitigation strategies.

Disclosures
Dr Pepine reports funding from the National Institutes of Health (NIH)/National Heart, Lung and Blood Institute–sponsored Women’s Ischemia Syndrome Evaluation (WISE), U01 HLO64829, and WISE Coronary Vascular Dysfunction, HL090957; the Patient-Centered Outcomes Research Institute (PCORI) OneFlorida Clinical Research Consortium; and the NIH/National Center for Advancing Translational Sciences award TR001427. Dr Wokhu has no conflicts to disclose.

References
1. van Loo HM, van den Heuvel ER, Schoevers RA, Anselmino M, Carney RM, Denollet J, Doyle F, Freedland KE, Grace SL, Hosseini SH, Parakh K, Pilote L, Rafanelli C, Roest AM, Sato H, Steeds RP, Kessler RC, Roest AM, Sato H, Steeds RP, Kessler RC, de Jonge P. Sex differences in platelet reactivity and cardiovascular and psychological response to mental stress in patients with stable ischemia heart disease: insight from the REMIT. J Am Coll Cardiol. 2014;65:1659–1678.
2. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, Duvernoy C, Walsh MN, Bairey Merz CN; ACC CVD in Women Committee. Emergence of nonobstructive coronary artery disease: a woman’s problem and need for change in definition on angiography. J Am Coll Cardiol. 2015;66:1918–1933.
3. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, Johnson BD, Sopko G, Bairey Merz CN. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women’s Ischemia Syndrome Evaluation) study. J Am Coll Cardiol. 2010;55:2825–2832.
4. Dakak N, Quyyumi AA, Eisenhofer G, Goldstein DS, Cannon RO III. Sympathetically mediated effects of mental stress on the cardiac microcirculation of patients with coronary disease. Am J Cardiol. 1995;76:125–130.
5. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dobrola S, Blankstein R, Rimoldi O, Camici PG, Dariulis MF. Effects of sex on coronary microvascular dysfunction and cardiovascular outcomes. Circulation. 2014;129:2518–2527.
6. Peix A, Trápaga A, Asen L, Ponce F, Infante O, Valiente J, Tornes J, Cabrera LO, Guerero I, Garcia EJ, Carrillo R, Garcia-Barredo D. Mental stress-induced myocardial ischemia in women with angina and normal coronary angiograms. J Nucl Cardiol. 2006;13:507–513.
7. Thurston RC, Johnson BD, Shufelt CL, Braunstein GD, Berga SL, Siancay FX, Pepine CJ, Bittner V, Reis SE, Thompson DV, Kelsey SF, Sopko G, Bairey Merz CN. Menopausal symptoms and cardiovascular disease mortality in the women’s ischemic syndrome evaluation (WISE). Menopause. In press.
8. Postrak V, Pyke KE. The impact of acute mental stress on vascular endothelial function: mechanisms and importance. Int J Psychophysiol. 2013;88:124–135.
24. Whittaker KS, Krantz DS, Rutledge T, Johnson DB, Wawrzyniak AJ, Bittner V, Eastwood J, Eteiba W, Cornell CE, Pepine CJ, Vido DA, Handberg E, Bairey Merz CN. Combining psychosocial data to improve prediction of cardiovascular disease risk factors and events: the NHLBI-sponsored Women’s Ischemia Syndrome Evaluation (WISE). Psychosom Med. 2012;74:263–270.

25. Jiang W, Velazquez EJ, Kuchibhatla M, Samad Z, Boyle SH, Kuhn C, Becker RC, Ortel TL, Williams RB, Rogers JG, O’Connor C. Effect of escitalopram on mental stress-induced myocardial ischemia: results of the REMIT trial. JAMA. 2013;309:2139–2149.

Key Words: Editorials • ischemia • ischemic heart disease • sex differences • stress • women