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Sex Differences in Platelet Reactivity and Cardiovascular and Psychological Response to Mental Stress in Patients With Stable Ischemic Heart Disease

Insights From the REMIT Study

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ABSTRACT

BACKGROUND Although emotional stress is associated with ischemic heart disease (IHD) and related clinical events, sex-specific differences in the psychobiological response to mental stress have not been clearly identified.

OBJECTIVES We aimed to study the differential psychological and cardiovascular responses to mental stress between male and female patients with stable IHD.

METHODS Patients with stable IHD enrolled in the REMIT (Responses of Mental Stress–Induced Myocardial Ischemia to Escitalopram) study underwent psychometric assessments, transthoracic echocardiography, and platelet aggregation studies at baseline and after 3 mental stress tasks. Mental stress–induced myocardial ischemia (MSIMI) was defined as the development or worsening of regional wall motion abnormality, reduction of left ventricular ejection fraction (LVEF) ≥8% by transthoracic echocardiography, and/or ischemic ST-segment change on electrocardiogram during 1 or more of the 3 mental stress tasks.

RESULTS In the 310 participants with known IHD (18% women, 82% men), most baseline characteristics were similar between women and men (including heart rate, blood pressure, and LVEF), although women were more likely to be nonwhite, living alone ($p < 0.001$), and unmarried ($p < 0.001$); they also had higher baseline depression and anxiety ($p < 0.05$). At rest, women had heightened platelet aggregation responses to serotonin ($p = 0.007$) and epinephrine ($p = 0.004$) compared with men. Following mental stress, women had more MSIMI (57% vs. 41%; $p < 0.04$), expressed more negative ($p = 0.02$) and less positive emotion ($p < 0.001$), and demonstrated higher collagen-stimulated platelet aggregation responses ($p = 0.04$) than men. Men were more likely than women to show changes in traditional physiological measures, such as blood pressure ($p < 0.05$) and double product.

CONCLUSIONS In this exploratory analysis, we identified clear, measurable, and differential responses to mental stress in women and men. Further studies should test the association of sex differences in cardiovascular and platelet reactivity in response to mental stress and long-term outcomes. (Responses of Myocardial Ischemia to Escitalopram Treatment [REMIT]; NCT00574847) (J Am Coll Cardiol 2014;64:1669–78) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

5HT = serotonin

ADP = adenosine diphosphate

BDI-TOT = Beck Depression Inventory II scale

BP = blood pressure

CABG = coronary artery bypass graft surgery

CESD = Center for Epidemiologic Studies Depression scale

CI = confidence interval

CVD = cardiovascular disease

HR = heart rate

IHD = ischemic heart disease

LVEF = left ventricular ejection fraction

MSIMI = mental stress-induced myocardial ischemia

OR = odds ratio

Despite therapeutic advances and greater awareness of the risk of cardiovascular disease (CVD) in women, outcomes and prognoses for women with CVD remain worse than those for men (1). This disparity suggests that sex-related differences in disease presentation, mechanisms, risk factors, and treatment may affect prognosis (2). Although some researchers have recently focused on characterizing the sex-specific influence of traditional coronary disease risk factors, these variables failed to completely account for the widely disparate presentations and CVD outcomes between men and women (3,4).

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The association of mental stress and CVD prognosis is well established (5), and mental stress is now gaining wide recognition as a potentially modifiable nontraditional CVD risk factor (6). Sex-specific differences in the psychobiological response to mental stress have not been clearly identified (7) and may provide valuable clues towards understanding the differential CVD risk in men and women. Conflicting data exist regarding sex-specific hemodynamic responses to stress, but conclusions are limited by small sample sizes (8–10).

We explored sex differences in response to mental stress across multiple important domains in CVD pathophysiology and prognosis (cardiovascular reactivity [11], platelet aggregation [12–15], and cardiovascular ischemic responses). We conducted this study in patients with clinically stable ischemic heart disease (IHD) who underwent baseline testing in the REMIT (Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment) trial (16–18).

METHODS

The study cohort examined for this analysis comprised patients who underwent baseline stress testing as a screening procedure for mental stress-induced ischemia (MSIMI) to allow for randomization in the REMIT trial. The REMIT trial (NCT00574847) study design (18) and primary results (17) were previously described. In brief, the REMIT study was a double-blind clinical trial that randomized subjects with stable coronary disease and MSIMI to either escitalopram treatment or placebo. Patients were invited to participate in screening stress-testing procedures if they had clinically stable IHD defined as the absence of a recent (<3 months) myocardial infarction, coronary artery bypass graft surgery (CABG), or any other revascularization procedures (e.g., percutaneous transluminal coronary angioplasty with or without stenting), unstable angina, and a plan for revascularization procedures. Patients were excluded if they had other significant medical comorbidities (i.e., cardiac, pulmonary, metabolic, renal, hepatic disease, or malignancy) or psychiatric diagnoses (i.e., bipolar spectrum mood disorders, psychotic disorders, current substance abuse/dependence or history within 6 months, and active suicidal ideation) that could interfere with participation in the trial intervention. Patients were also excluded if they had severe psychiatric symptoms, were pregnant, or were using antidepressants, including selective serotonin reuptake inhibitors. The protocol was reviewed and approved by the Duke University Health System Institutional Review Board. All participants provided written, voluntary informed consent before participating in any assessment.

MENTAL STRESS AND EXERCISE TESTING. Study subjects underwent 2 sessions of assessment and testing, which included a psychiatric assessment and

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