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Young women post-MI have higher plasma concentrations of interleukin-6 before and after stress testing

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ABSTRACT

Objectives: Young women have poorer prognosis after myocardial infarction (MI) and a higher rate of mental stress-induced ischemia compared with similarly aged men. A higher inflammatory status may help explain these sex differences.

Methods: We examined 98 patients (49 women and 49 men) age 18–59 years with recent MI (past 6 months). Women and men were matched for age, type of MI, and time since MI. Interleukin 6 (IL-6) concentrations were measured at baseline, after mental stress using a speech task, and after exercise/pharmacologic stress (60 and 90 min). Depressive symptoms were measured with the Beck Depression Inventory (BDI-II) and angiographic coronary artery disease (CAD) severity was quantified with the Gensini score. Single-photon emission computed tomography (SPECT) was used to obtain a computerized measurement of stress-induced ischemia (summed difference score, or SDS) and determine whether severity of stress-induced ischemia affects the inflammatory response to stress. Analysis was stratified by the median age of 50. Geometric mean concentrations of IL-6 were obtained from general linear regression models.

Results: In both age groups, women had less angiographic CAD and a similar level of conventional risk factors compared with men. Despite this, baseline IL-6 geometric means before both mental and physical stress were twice as high in women $\leqslant$50 years of age compared to age-matched men (3.8 vs. 1.8 pg/mL, $p = 0.001$, across both conditions), while they were similar in women and men age >50 years (2.3 vs. 2.2 pg/mL, $p = 0.83$). After mental stress, IL-6 concentrations increased in both women and men in a similar fashion and remained twice as high in women $\leqslant$50 years than men at both 60 min (5.4 vs. 2.6 pg/mL, $p = 0.002$) and 90 min (5.9 vs. 3.4 pg/mL, $p = 0.01$). No significant difference was found between women and men >50 years of age at any time point after mental stress. Results were similar for physical stress. After accounting for SDS, IL-6 concentrations in young women remained higher after both mental and physical stress. Baseline IL-6 concentrations were not significantly related to inducible ischemia.

Conclusions: After MI, young women aged 50 years or younger, compared with age-matched men, have remarkably higher concentrations of inflammation at baseline and after both mental and physical stress, with a similar inflammatory response to both stressors. Sustained concentrations of inflammation in young women, not their response to stress, may contribute to their adverse outcomes post-MI.

1. Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the United States (Go et al., 2014). Substantial differences exist in the outcome of CAD by sex and age, as numerous studies have demonstrated that young and middle-aged women (<50 years) who experience an acute myocardial infarction (AMI),

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have poorer outcomes than men of the same age (Andrikopoulos et al., 2006; Koek et al., 2006; Vaccarino et al., 1999, 2009). This is in spite of the fact that women have less severe CAD and are more likely to have preserved systolic function and smaller infarcts when compared with their male counterparts (Rosengren et al., 2001; Vaccarino et al., 1999). The reasons for these differences are not yet clear.

Psychological stress can act as a trigger of acute coronary syndromes, such as a myocardial infarction (MI), in patients with underlying coronary artery disease (CAD) (Krantz et al., 1996; Mittleman et al., 1993, 1995). The pathophysiological mechanisms explaining the effects of stress on CAD risk may include sympathetic nervous system (SNS)-mediated increases in catecholamines and in cardiac demand, as well as plaque instability and myocardial ischemia (Krantz et al., 1996; Mittleman et al., 1993, 1995). Psychological stress also leads to increased inflammation in both healthy (Edwards et al., 2006b; Steptoe et al., 2002) and CAD populations (Kop et al., 2008), which may mediate the effects of stress on CAD incidence and progression (Kop, 2003). We recently found that young post-MI women (50 years old or younger) experience a higher rate of mental stress-induced myocardial ischemia (MSIMI) than age-matched men (Vaccarino et al., 2014), a difference that was not explained by traditional CAD risk factors. Women have been shown to exhibit higher circulating concentrations of inflammatory markers than men (Khera et al., 2005; Woloshin and Schwartz, 2005) and sex differences in cytokine response to physical or psychological stress have been described (Edwards et al., 2006a,b); so it is possible that sex differences in inflammation are implicated and potentially translate into poorer outcomes in young women after MI. To our knowledge however, no study has examined sex or age differences in the inflammatory response to psychological stress in patients with CAD.

In a sample of young and middle aged (<50 years) men and women who had experienced a recent MI (past 6 months), we examined changes in interleukin-6 (IL-6) concentrations in the circulation before and after a standardized mental stress challenge in order to investigate the role that sex and age play in the inflammatory response to stress in this patient population. Since patients underwent myocardial perfusion imaging with both mental stress and a physical stressor (exercise or pharmacological stress test), we were also able to examine whether sex differences in inflammatory responses were confounded by myocardial ischemia.

2. Methods

2.1. Participants

The methods of the Myocardial Infarction and Mental Stress Study (MIMS) were described before (Vaccarino et al., 2014). Briefly, between July 2009 and April 2012, 98 patients were enrolled who were between the age of 38 and 59 years and had a documented history of MI within the previous 6 months. Men and women were matched for age (±2 years), type of MI (ST-elevation MI or non-ST-elevation MI) and time since the MI (±2 months). The diagnosis of MI was verified by medical record review based on standard criteria of troponin level increase and ECG changes (Thygesen et al., 2007). Subjects were excluded if they had unstable angina or acute MI within the past week, or a severe comorbid medical or psychiatric disorder that could interfere with study results, such as cancer, renal failure, current alcohol or substance abuse or schizophrenia. Subjects were also excluded if they weighed over 400 lb (due to limits on the weight bearing of the nuclear stress test equipment), if they were pregnant or breast-feeding, or if they were currently using postmenopausal hormone therapy or psychotropic medications other than antidepressants. Finally, patients were excluded if they were unable to exercise on a treadmill, based on a score <5 METs (Metabolic Equivalents) on the Duke Activity Status Index (DASI), which identifies patients who cannot exercise to heart rate targets (Hlatky et al., 1989).

2.2. Study design

Subjects underwent two separate days of testing. All testing was done after an overnight fast, and anti-ischemic medications, including beta-blockers, calcium channel blockers and long-acting nitrates were held for 24 h prior to testing. Patients were not included in the study if they had symptoms or signs of acute illness. Sociodemographic and psychosocial data were collected at the first visit prior to the stress testing. At the end of the study protocol, medical records were abstracted for clinical information, including ejection fraction and catheterization data. The study protocol was approved by the Emory University Institutional Review Board, and informed consent was obtained from all participants.

2.3. Mental and physical stress procedures

The procedures for mental and physical stress testing have previously been described (Vaccarino et al., 2014). Briefly, mental and physical stress testing was conducted on two separate days, within 1 week of each other; the order of the stressors was counterbalanced. For mental stress, participants were asked to imagine a real-life stressful situation, such as a close relative been mistreated in a nursing home, and asked to make up a realistic story around this scenario. They were given 2 min to plan the story and prepare a statement and 3 min to present it in front of a video camera and an audience wearing white coats. For physical stress, subjects were submitted to a Bruce protocol by walking on the treadmill, with exercise target set at 85% of maximum predicted heart rate based on the patient's sex and age. For subjects ($n = 16$) who were unable to reach the heart rate target despite scoring $\geqslant 5$ METs on the DASI during screening, we performed a pharmacological stress test with regadenoson (Astellas, Northbrook, IL), an adenosine receptor agonist. Subjective ratings of distress were measured before and after mental stress with the Subjective Units of Distress Scale (SUDS). The SUDS measures distress on a linear scale of 0–100, with 100 being the highest level of distress (Wolpe, 1973).

2.4. Measurements

2.4.1. Measurement of inflammatory responses

IL-6 was tested from blood samples collected before (two separate baseline measurements) and after mental and physical stress conditions. Blood samples were obtained from a catheter placed in the arm and collected in EDTA tubes, placed immediately on ice, and centrifuged at 4 °C for 10 min at 3000 rpm. IL-6 was tested from plasma samples aliquoted from whole blood collected before, 60 and 90 min after mental and physical stress. Plasma collection time points were selected based on prior studies of physical and mental stress testing (Edwards et al., 2006b; Mendham et al., 2011; Moldoveanu et al., 2000; Steptoe et al., 2001), including work by us (Pace et al., 2006; Pace et al., 2009, 2010), indicating that the IL-6 response to stress becomes most apparent 1 h after mental and physical stress onset. IL-6 was assessed using commercially available ELISA kits from R and D Systems (R & D) Systems, Minneapolis, MN.

2.4.2. Myocardial perfusion imaging

Subjects underwent three SPECT myocardial perfusion imaging scans following injection of sestamibi radiolabelled with technetium-99m ([^{99m}Tc]) ([^{99m}Tc]-sestamibi), at rest, during mental stress, and during physical stress on a dedicated ultra-fast solid-