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## Sex Differences in Mental Stress-Induced Myocardial Ischemia in Patients With Coronary Heart Disease

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**Background**—Emerging data suggest that young women with coronary heart disease (CHD) are disproportionately vulnerable to the adverse cardiovascular effects of psychological stress. We hypothesized that younger, but not older, women with stable CHD are more likely than their male peers to develop mental stress-induced myocardial ischemia (MSIMI).

**Methods and Results**—We studied 686 patients (191 women) with stable coronary heart disease (CHD). Patients underwent  $^{99m}\text{Tc}$ -sestamibi myocardial perfusion imaging at rest and with both mental (speech task) and conventional (exercise/pharmacological) stress testing. We compared quantitative (by automated software) and visual parameters of inducible ischemia between women and men and assessed age as an effect modifier. Women had a more-adverse psychosocial profile than men whereas there were few differences in medical history and CHD risk factors. Both quantitative and visual indicators of ischemia with mental stress were disproportionately larger in younger women. For each 10 years of decreasing age, the total reversibility severity score with mental stress was 9.6 incremental points higher (interaction,  $P<0.001$ ) and the incidence of MSIMI was 82.6% higher (interaction,  $P=0.004$ ) in women than in men. Incidence of MSIMI in women  $\leq 50$  years was almost 4-fold higher than in men of similar age and older patients. These results persisted when adjusting for sociodemographic and medical risk factors, psychosocial factors, and medications. There were no significant sex differences in inducible ischemia with conventional stress.

**Conclusions**—Young women with stable CHD are susceptible to MSIMI, which could play a role in the prognosis of this group. (*J Am Heart Assoc.* 2016;5:e003630 doi: 10.1161/JAHA.116.003630)

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

Coronary heart disease (CHD) is the major cause of death in American women as it is in men, but despite considerable scientific advances, much remains to be learned about the unique characteristics of this disease in women. Young and middle-aged women, in particular, have been under-represented in research studies of cardiovascular

disease. For over a decade now, studies have shown that young women have higher mortality and complication rates after an acute myocardial infarction (MI) compared to men of similar age, but these differences remain unexplained.<sup>1</sup> There is also a concern that prevention efforts may have been less efficacious in young women in recent years.<sup>2</sup> Hospitalization rates for MI are on the rise in women  $\leq 55$  years, in contrast to other demographic groups,<sup>3,4</sup> and the prehospital case fatality of MI<sup>5</sup> and overall CHD mortality<sup>6</sup> have recently declined less in this segment of the population. The reasons for these variations are not clear but may be attributed, at least in part, to understudied or under-recognized risk factors.

Emotional stress is emerging as an important, albeit unappreciated, risk factor for cardiovascular disease in young women. Psychosocial factors are powerful predictors of cardiovascular disease incidence and mortality in young women from the general population<sup>7–10</sup> and of recurrent events and delayed recovery in young women with CHD.<sup>11,12</sup> This group is characterized by relatively high rates of economic disadvantage, depression, early life adversities, and perceived stress compared with men and older patients.<sup>11–14</sup> As a whole,

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these data suggest a role of emotional factors on cardiovascular risk and outcome in young women, but objective evidence of this vulnerability is still insufficient.

Mental stress testing represents an objective, standardized method for assessing the cardiovascular effects of acute emotional stress exposure. Mental stress-induced myocardial ischemia (MSIMI) can be provoked in the laboratory in up to approximately half of patients with CHD and correlates with myocardial ischemia in daily life.<sup>15</sup> MSIMI carries prognostic information similar to that of ischemia induced by conventional stress testing,<sup>16</sup> despite not being related to severity of obstructive coronary disease.<sup>17</sup> In a previous study of post-MI patients, we reported that women  $\leq 50$  years, but not older women, had a doubling of the rate of MSIMI compared to age-matched men.<sup>13</sup> However, this study was based on a small sample of patients younger than 60 years, limiting our ability to assess whether young women are uniquely at risk for this phenomenon. In the current study, based on a large sample with broad age range, our goal was to investigate whether young women with CHD are more likely to develop MSIMI than men and older patients. We further contrasted the results with a control condition of conventional stress testing (a standard exercise or pharmacological stress test).

## Methods

### Subjects and Design

Between July 2009 and July 2014, the Mental Stress Ischemia Mechanisms and Prognosis Study (MIPS) enrolled 695 patients with a diagnosis of stable CHD from Emory University–affiliated hospitals and clinics. The main objectives of MIPS were to clarify mechanisms and prognosis of mental stress-induced ischemia assessed with myocardial perfusion imaging in patients with CHD. Criteria for CHD included: (1) abnormal coronary angiography or intravascular ultrasound demonstrating atherosclerosis with at least luminal irregularities; (2) previous percutaneous or surgical coronary revascularization; (3) documented MI; or (4) positive exercise or pharmacological nuclear stress test or electrocardiographic exercise stress test. Patients were excluded if they were pregnant, if they had been hospitalized in the previous week for unstable angina, decompensated heart failure, or MI; had severe psychiatric conditions, such as schizophrenia or current alcohol or substance abuse; or had active malignancy or end-stage renal disease or other severe medical problems expected to shorten life expectancy to  $< 5$  years.

Study subjects underwent two 1-day single-photon emission computed tomography (SPECT) imaging studies, one with mental stress and one with exercise or pharmacological stress, within 1 week of each other. We withheld anti-ischemic medications for at least 24 hours before testing. The Emory

University Institutional Review Board approved the protocol, and all participants provided written informed consent.

### Mental Stress Procedure

After 30 minutes of rest, mental stress was induced by a standardized public speaking task as previously described.<sup>17,18</sup> Patients were asked to imagine a real-life stressful situation, in which a close relative was been mistreated in a nursing home, and asked to make up a realistic story around this scenario. They were given 2 minutes to prepare a statement and then 3 minutes to present it in front of a video camera and an audience wearing white coats. We recorded blood pressure and heart rate at 5-minute intervals during the resting phase and at 1-minute intervals during the mental stress task, and calculated the rate-pressure product. We also obtained subjective ratings of distress with the Subjective Units of Distress Scale<sup>19</sup> on a linear scale of 0 to 100.

### Myocardial Perfusion Imaging

Subjects underwent 3 SPECT myocardial perfusion imaging scans after injection of sestamibi radiolabeled with technetium-99 m ( $^{99m}\text{Tc}$ ), at rest, during mental stress, and during conventional stress (10–14 mCi for rest imaging and 30–40 mCi for stress imaging, based on weight). Testing was done in 2 separate days up to 1 week apart on a dedicated SPECT camera (Philips Cardio MD) without attenuation correction. On the mental stress day,  $^{99m}\text{Tc}$ sestamibi was injected 1 minute after onset of the public speech task. On the conventional stress day, the radioisotope injection was given at peak exertion or immediately after the regadenoson (Abbott, Chicago, IL) injection for pharmacological stress testing.

We assessed myocardial perfusion using a 17-segment model both by the automated function in the Emory Cardiac Toolbox (ECTb)<sup>20</sup> and by visual analysis. We quantified severity of ischemia by the ECTb as a total reversibility severity score (sum of the number of SDs in the reversibility map above the mean of a normal database) and as total reversibility extent (magnitude of stress-induced perfusion deficit as percent of the left ventricle [LV]). Reversibility  $\geq 2\%$  is considered abnormal.<sup>21,22</sup> Quantitative analysis has excellent clinical and prognostic value, which is similar to expert visual analysis.<sup>22,23</sup>

Two experienced readers (P.R. and F.E.) performed visual interpretation blinded to stress test type and clinical data; disagreement was resolved by consensus. Each myocardial segment was scored from 0 to 4, with 0 being normal, 1 possibly normal, 2 definitely abnormal, 3 severely abnormal, and 4 no perfusion. We defined myocardial ischemia as a new perfusion abnormality (a score of  $\geq 2$  in any segment), or worsening of pre-existing abnormality by at least 2 points in a

single segment, or by at least 1 point in 2 or more contiguous segments. In addition to individual segment scores, we calculated summed scores in a conventional fashion, including a summed stress score, a summed rest score, and a summed difference score (SDS), the latter representing a semiquantitative measure of inducible ischemia.<sup>23</sup> We calculated percent ischemic myocardium as  $(SDS/68) \times 100$ .

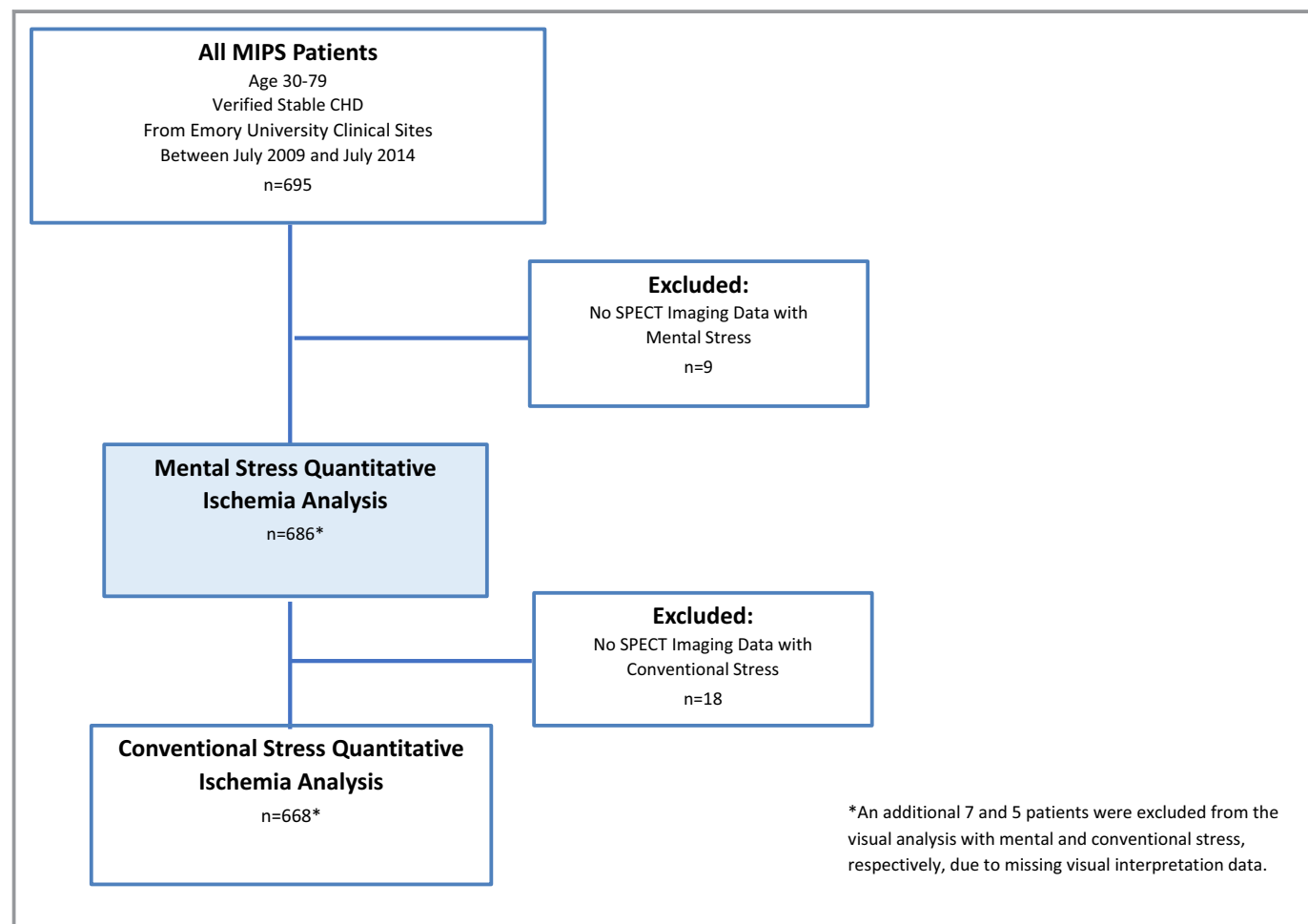
The use of both automated and visual approach provided complementary information in our study. Visual assessment is more accepted clinically, but it is not entirely blinded to the sex of the patient because of breast silhouette in visual images. The ECTb, on the other hand, provides an operator-independent assessment of perfusion abnormalities free of potential sex-related bias.

### Other Measurements

A research nurse obtained detailed sociodemographic and medical history information, including medication use, and

measured weight and height to calculate the body mass index (BMI). Trained personnel abstracted medical records for clinical and angiographic data. Obstructive coronary artery disease (CAD) was defined as  $\geq 50\%$  lumen stenosis. CAD severity was quantified with the Gensini scoring method, which uses a nonlinear point system for degree of luminal narrowing that weighs lesions according to specific coronary tree locations to take into account prognostic significance.<sup>24</sup>

We used validated instruments to assess behavioral, social, and health status information. Angina symptoms were measured with the Angina Frequency Subscale of the Seattle Angina Questionnaire,<sup>25</sup> which assesses chest pain over the past 4 weeks. Depressive symptoms were assessed with the Beck Depression Inventory-II,<sup>26</sup> a reliable and valid self-report measure that has been widely used in cardiac populations. In addition, we administered the Structured Clinical Interview for DSM IV<sup>27</sup> to derive a current and lifetime diagnosis of major depression and other psychiatric diagnoses. Childhood



**Figure 1.** Diagram of patient selection for the main analysis (n=686) and additional analyses in the study. Slightly different numbers were included in subgroup analyses because of missing values. CHD indicates coronary heart disease; SPECT, single-photon emission computed tomography.

**Table 1.** Sex Differences in Patient Characteristics, and Interaction Between Sex and Age for Each Characteristic

	Mean (SD) or Percent All Patients		P Value	P for Sex By Age Interaction*
	Women N=191	Men N=495		
<b>Demographic factors</b>				
Age, y, mean (SD)	62.6 (9.4)	63.0 (9.1)	0.65	—
34 to 50	21 (11.0)	47 (9.5)	0.91	—
51 to 60	54 (28.3)	148 (29.9)		
61 to 70	70 (36.7)	183 (37.0)		
71 to 79	46 (24.1)	117 (23.6)		
Black race, %	43.4	25.2	<0.001	0.36
Married, %	46.1	72.1	<0.001	0.37
Education, total school years, mean (SD)	14.3 (3.1)	15.2 (3.5)	0.001	0.52
Income below poverty level ( $\leq$ \$20 000), %	23.0	12.9	0.001	0.23
<b>Lifestyle, medical history and CHD risk factors</b>				
Current smoking, %	15.7	14.4	0.67	0.38
BMI, mean (SD)	30.4 (6.3)	29.4 (4.9)	0.055	0.68
Previous myocardial infarction, %	37.7	37.4	0.94	0.94
History of heart failure, %	16.2	13.5	0.37	0.52
Angina in past 4 weeks, %	41.6	24.2	<0.001	0.04
Hypertension, %	79.1	75.6	0.33	0.45
Dyslipidemia, %	78.0	83.4	0.10	0.09
Diabetes mellitus, %	37.7	30.5	0.07	0.51
Previous revascularization, %	78.0	76.2	0.61	0.66
<b>Psychosocial factors</b>				
Beck depression inventory, mean (SD)	10.2 (8.8)	7.7 (8.2)	<0.001	0.54
Lifetime history of major depression, %	36.6	22.3	<0.001	0.36
<b>Stressful events before age 18, mean (SD)</b>				
General trauma	2.8 (2.3)	2.8 (2.3)	0.84	0.49
Physical abuse	1.3 (1.4)	2.2 (1.6)	<0.001	0.17
Emotional abuse	1.5 (1.8)	1.0 (1.6)	0.002	0.47
Sexual abuse	1.1 (1.7)	0.5 (1.1)	<0.001	0.01
Perceived stress scale	14.5 (8.1)	11.6 (7.2)	<0.001	0.73
<b>State-trait anxiety inventory</b>				
State	32.6 (11.1)	30.6 (11.0)	0.03	0.63
Trait	35.0 (10.8)	32.6 (10.4)	0.007	0.90
<b>Current medications (%)</b>				
Statins	83.2	86.0	0.34	0.25
Beta-blockers	77.5	73.7	0.30	0.21
ACE Inhibitors	34.7	49.6	<0.001	0.80
Aspirin	83.8	87.2	0.24	0.88
Antidepressants	32.5	19.0	<0.001	0.83
Anxiolytics	10.5	7.7	0.24	0.98

Continued

Table 1. Continued

	Mean (SD) or Percent All Patients		P Value	P for Sex By Age Interaction*
	Women N=191	Men N=495		
Baseline imaging data and CAD severity indicators (SD)				
Rest total severity score (automated analysis)	210 (309)	254 (307)	0.09	0.19
Summed rest score (visual analysis)	3.5 (7.0)	5.7 (9.2)	<0.001	0.18
Resting LV ejection fraction	74.8 (13.9)	66.2 (12.8)	<0.001	0.048
Gensini score for angiographic CAD severity <sup>†,‡</sup>	17.6 (4.0)	24.5 (3.6)	0.006	0.59
Obstructive CAD (lumen stenosis $\geq 50\%$ ) <sup>‡</sup>	86.6	92.1	0.04	0.27

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; LV, left ventricle.

\*Age as a continuous variable.

<sup>†</sup>Geometric means.

<sup>‡</sup>Angiographic data were available in 594 patients (87%). There were no differences in missing angiographic data by sex or age.

traumatic experiences were assessed by means of the Early Trauma Inventory, a validated measure of physical, emotional, and sexual abuse and general traumatic events before age 18 years.<sup>28</sup> The score represents the number of traumatic exposures in each category. We also administered the Cohen's Perceived Stress Scale,<sup>29</sup> a 10-item survey of general stress validated in multiethnic populations, and the State-Trait Anxiety Inventory, a 40-item questionnaire to measure anxiety as an emotional state or a personality trait.<sup>30</sup>

## Statistical Analysis

The main objective of the statistical analysis was to assess the role of age as an effect modifier of sex differences in proclivity to develop MSIMI, that is, whether there was a significant interaction between sex and age on quantitative and visual parameters of MSIMI. We conducted similar analyses for conventional stress ischemia as a control condition. Our main analysis used age as a continuous

Table 2. Sex Differences in Changes in Hemodynamic Parameters and Subjective Distress with Mental Stress, and Interaction Between Sex and Age

	Mean Change (SD) All Patients		P Value	P for Sex By Age Interaction*
	Women N=191	Men N=495		
Systolic blood pressure, mm Hg (SD)				
Stress reactivity method 1 <sup>†</sup>	39.9 (17.9)	40.6 (18.1)	0.64	0.69
Stress reactivity method 2 <sup>‡</sup>	24.1 (16.6)	26.2 (15.5)	0.13	0.99
Diastolic blood pressure, mm Hg (SD)				
Stress reactivity method 1 <sup>†</sup>	23.9 (10.4)	24.5 (10.6)	0.48	0.33
Stress reactivity method 2 <sup>‡</sup>	12.1 (8.6)	13.2 (8.4)	0.12	0.60
Heart rate, beats/min (SD)				
Stress reactivity method 1 <sup>†</sup>	18.2 (11.2)	16.8 (10.9)	0.14	0.68
Stress reactivity method 2 <sup>‡</sup>	12.2 (9.2)	10.8 (9.2)	0.07	0.97
Rate-pressure product (SD)				
Stress reactivity method 1 <sup>†</sup>	5094 (2624)	4904 (2731)	0.41	0.98
Stress reactivity method 2 <sup>‡</sup>	3598 (2350)	3408 (2295)	0.33	0.80
Subjective units of distress scale (SD) <sup>§</sup>	11.9 (24.2)	9.7 (16.7)	0.26	0.28

\*Age as a continuous variable.

<sup>†</sup>Difference between maximum value during stress and minimum value during rest.

<sup>‡</sup>Difference between average value during stress and average value during rest.

<sup>§</sup>Difference between posttest and pretest values. A positive value indicates higher distress with mental stress.

**Table 3.** Unadjusted Sex Differences in Myocardial Ischemia Parameters, in All Patients and Per 10-Year Decrement in Age

	Mean (SE) or Percent All Patients		P Value	Mean or Percent Difference Comparing Women to Men Per 10-Year Decrement in Age*	95% CI	P for Sex by Age Interaction
	Women	Men				
<b>Mental stress</b>						
Quantitative automated analysis						
Total reversibility severity score, mean	12.1 (2.0)	6.6 (1.2)	0.02	9.6	4.7, 14.4	<0.001
% LV with inducible ischemia, mean	1.04 (0.15)	0.58 (0.09)		0.72	0.36, 1.08	
Abnormal reversibility ( $\geq 2\%$ of LV), %	14.7	9.3	0.04	63.3	2.6, 159.8	0.039
Visual analysis						
Summed difference score, mean	0.88 (0.15)	0.73 (0.09)	0.37	0.64	0.28, 1.00	<0.001
% LV with inducible ischemia, mean	1.29 (0.22)	1.07 (0.13)		0.94	0.41, 1.47	
Myocardial ischemia, %	14.4	16.5	0.52	82.6	21.3, 174.7	0.004
<b>Conventional stress</b>						
Quantitative automated analysis						
Total reversibility severity score, mean	38.8 (5.0)	28.9 (3.1)	0.09	4.5	-7.9, 17.0	0.48
%LV with inducible ischemia, mean	3.45 (0.38)	2.49 (0.24)		0.39	-0.57, 1.34	
Abnormal reversibility ( $\geq 2\%$ of LV), %	35.1	28.8	0.11	8.9	-20.5, 42.8	0.54
Visual analysis						
Summed difference score, mean	2.27 (0.33)	2.63 (0.20)	0.34	0.62	-0.20, 1.44	0.14
% LV with inducible ischemia, mean	3.33 (0.49)	3.87 (0.30)		0.92	-0.29, 2.1	
Myocardial ischemia, %	31.5	36.1	0.27	31.6	1.6, 70.5	0.04

LV indicates left ventricle.

\*Age was included as a continuous variable. The effects shown were calculated from the interaction between sex and age.

variable, with effects scaled per 10 years age decrements. We fitted linear and logistic regression models (depending on the distribution of the response variable) to assess sex differences in quantitative and visual indicators of ischemia and test for the interaction between sex and age after adjusting for a set of factors that were considered a priori as either possible confounders or mediators. Because results across various indicators of ischemia were similar, multivariable analyses are shown for 2 representative parameters: the total reversibility severity score from the quantitative analysis and ischemia as a binary variable from the visual analysis. Using hierarchical models, we sequentially adjusted for sociodemographic and lifestyle characteristics, clinical risk variables and CAD severity, depressive symptoms, and medication use. In models predicting ischemia with mental stress, we also evaluated whether the results were independent of ischemia with conventional stress. Finally, in order to more clearly describe the interaction effect, and because our previous research showed that women  $\leq 50$  years were especially at risk for MSIMI,<sup>13</sup> we also reported the main results according to 4 decades of age:  $\leq 50$  years, 51 to 60 years, 61–70 years, and  $>70$  years. In these analyses, we compared men and

women in 4 age groups, for a total of 4 comparisons. Using the Bonferroni correction,  $P \leq 0.0125$  should be interpreted as statistically significant in the age-stratified analysis. All analyses were conducted using the Statistical Analysis System (SAS; version 9.3; SAS Institute Inc., Cary, NC).

## Results

### Study Sample

In the enrollment period, 695 patients were enrolled; of these, 686 participants (98.7%), 191 women and 495 men, had usable SPECT imaging data with mental stress and were included in the analysis. A flow chart of patient selection for the current study is shown in Figure 1. Mean age was 63 years in both women and men, with a range of 34 to 79 years. Women showed a more adverse psychosocial risk profile, but a similar or better clinical risk profile than men (Table 1); they were more often African American, unmarried, less educated, and with income below the poverty level. Women also exhibited higher levels of symptoms of depression, anxiety and perceived stress, were more likely to meet

clinical criteria for major depression, and had higher scores of emotional and sexual abuse in childhood, although physical abuse was more common in men. Women reported more angina and lower functional status and more often had a history of diabetes mellitus, but other CHD risk factors and previous cardiovascular history were similar. Baseline imaging data were more favorable in women than in men, given that women showed fewer resting perfusion abnormalities, a higher ejection fraction, a lower angiographic CAD severity score, and a lower rate of obstructive CAD ( $\geq 50\%$  lumen stenosis). Sex differences in patient characteristics did not vary significantly by age with the exception of angina and history of sexual abuse, which were more common in younger women. Most of the women 50 years or younger (62.5%) were premenopausal by self-report, whereas only 1 woman between 51 and 60 years of age and none older than 60 reported not to have yet reached menopause.

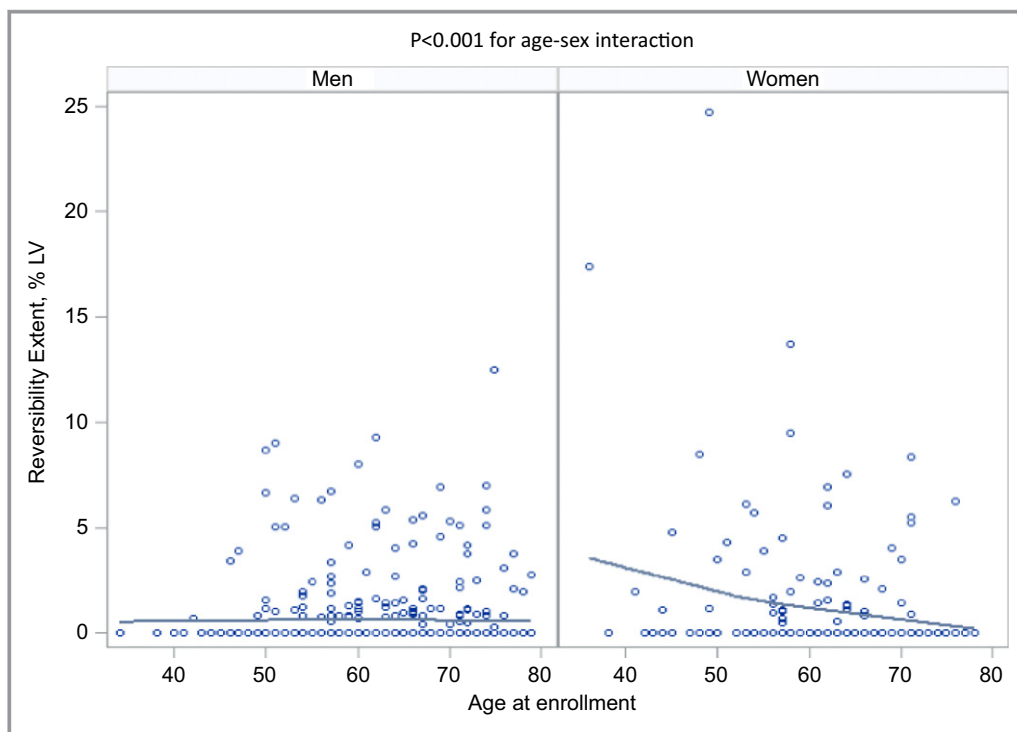
### Hemodynamic Reactivity

As shown in Table 2, hemodynamic responses to mental stress were similar in women and men for both methods of reactivity calculation and across age. Both women and men achieved adequate hemodynamic responses to mental stress. Women and men also showed comparable subjective ratings of distress with mental stress.

### Myocardial Perfusion

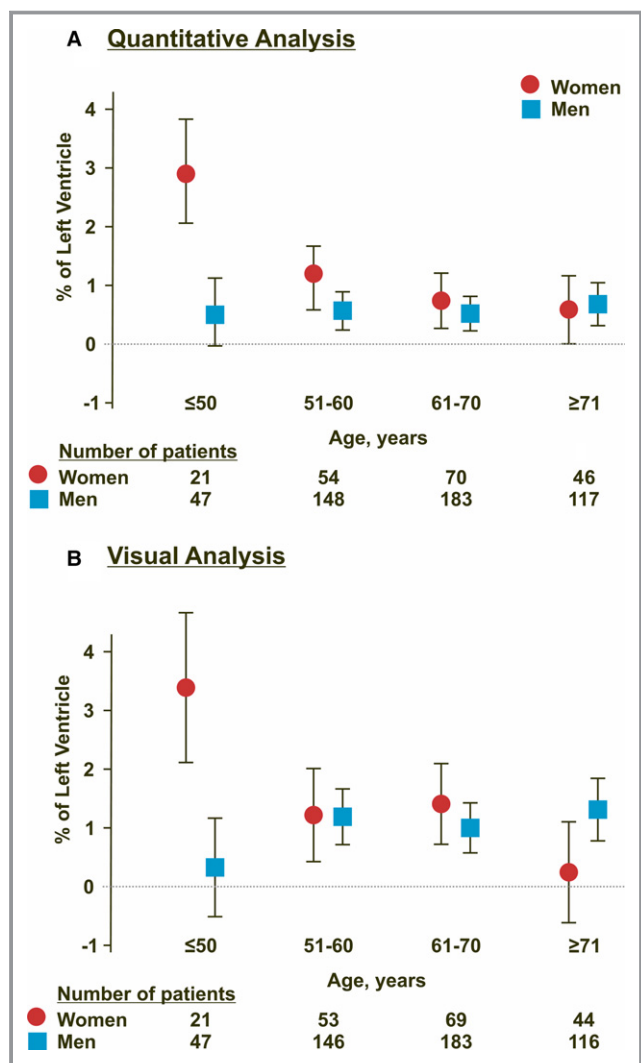
Of the 686 patients with SPECT imaging data with mental stress, 668 (97.4%) also had usable data with conventional stress. Of these, 471 (70.5%) underwent a treadmill stress test and the rest underwent a pharmacological stress test. Women were more likely to receive a pharmacological stress test than men (38.9% vs 25.9%).

Overall, the rate of inducible ischemia was higher with conventional stress (34.8%) than with mental stress (15.9%). In the whole sample, women tended to show more ischemia, both with mental stress and conventional stress, compared to men (Table 3). However, sex differences in ischemia with mental stress, but not conventional stress, varied by age: Both quantitative and visual indicators of ischemia with mental stress showed larger differences between women and men in younger than in older patients. For each 10 years of decreasing age, the total reversibility severity score with mental stress was 9.6 incremental points higher in women, corresponding to 0.72% more LV myocardium with ischemia (interaction,  $P < 0.001$ ), and the incidence of MSIMI was 82.6% higher in women (interaction,  $P = 0.004$ ). An illustration of the interaction effect using age as a continuous variable is shown in Figure 2. To ease interpretation, these results are depicted by age group in Figure 3. Women  $\leq 50$  years had elevated markers of ischemia with mental stress compared to men; their percent LV with inducible ischemia was over 5-fold that



**Figure 2.** Inducible myocardial ischemia with mental stress according to sex and age as a continuous variable. Ischemia was expressed as percent of ischemic myocardium derived by automated quantitative analysis. LV indicates left ventricle.





**Figure 3.** Inducible myocardial ischemia with mental stress according to sex and age group. Young women ( $\leq 50$  years) showed more ischemia with mental stress than any of the other groups. Ischemia was expressed as percent of ischemic myocardium and was derived with 2 separate methods: automated quantitative analysis (A) and visual analysis (B). In both analyses, the interaction between sex and age was highly significant ( $P < 0.001$ ), and the comparison between women and men in the group  $\leq 50$  was also highly significant ( $P < 0.0001$ ). Error bars indicate confidence intervals.

of men. Expressed as presence or absence of MSIMI, 33% of women  $\leq 50$  years of age developed MSIMI compared to only 8% of men of similar age (data not shown). Not only had young women more ischemia with mental stress than men, but they also had significantly more ischemia with mental stress than older women ( $P < 0.001$  for all quantitative parameters of reversibility). In fact, MSIMI was inversely associated with age in women, but not in men (Figures 2 and 3). In contrast, perfusion data with conventional stress testing showed only modest differences between women and men with little variation by age (Table 3).

In all multivariable models, the interaction effect remained substantially unchanged (Table 4). After adjusting for sociodemographic and lifestyle characteristics, clinical risk variables, CAD severity, depressive symptoms, and medication use, the total reversibility severity score was 10 points higher, and the odds for MSIMI were more than doubled, in women compared to men for each 10-year decrement in age. Adjusting for ischemia with conventional stress did not substantially affect the results.

## Discussion

In a large sample of patients with stable CHD, we demonstrated large variations in the likelihood of developing MSIMI based on sex and age. Using both automated and visual image analysis, younger women, especially those  $\leq 50$  years, exhibited more evidence of ischemia with mental stress than men of similar age. The incidence of MSIMI in this group was over 3-fold higher than their male counterparts and was also higher than older women and men. Notably, young women showed an elevated rate of ischemia also with conventional stress testing, but the difference with men was less marked. These results suggest a vulnerability toward MSIMI in women with early-onset CHD and are consistent with our previous findings in a sample of young survivors of an acute MI.<sup>13</sup>

Given that most previous studies of MSIMI have included predominantly men,<sup>15,16</sup> until recently little was known about MSIMI in women. In the REMIT trial of stable CHD patients, which assessed MSIMI with echocardiography, women had a 39% higher rate of MSIMI than men.<sup>31</sup> On the other hand, York et al.<sup>32</sup> did not find sex differences in MSIMI assessed with a protocol similar to ours. These studies included predominantly older patients and few women. Ours is the first investigation with a sufficiently large sample to examine this question in a rigorous way.

The precise mechanisms for the sex difference in MSIMI require further investigation. In our study, as in previous ones,<sup>11,13,31</sup> women had a higher burden of psychosocial risk factors than men, which may signal a heightened physiological susceptibility to stress. Hemodynamic responses to stress are not likely to play a role, however, given that women in our study did not show larger changes in blood pressure and heart rate with stress than men, similarly to previous work.<sup>31,32</sup> Women also did not report higher subjective distress with mental stress. Others, however, have described a tendency for women to express more-negative emotions and less-positive emotions, together with a higher platelet reactivity with mental stress, compared to men.<sup>31</sup> A recent study reported a greater increase in depressed mood and feelings of social disconnection in healthy young women compared to men after exposure to an inflammatory challenge with endotoxin, even though the inflammatory response was similar.<sup>33</sup> Similarly, in a previous

**Table 4.** Multivariable Analysis of the Variation of the Effect of Sex on Myocardial Ischemia Parameters With Mental Stress Per 10-Year Decrement in Age\*

Total Reversibility Severity Score (Quantitative Analysis)			
	Mean Difference in Women Versus Men Per 10-Year Decrement in Age	95% CI	P for Sex by Age Interaction
Adjusted for sociodemographic and lifestyle factors <sup>†</sup>	10.1	5.1, 15.0	<0.001
Adjusted for the above plus CHD risk factors, other medical history and CAD severity <sup>‡</sup>	9.5	4.5, 14.4	<0.001
Adjusted for the above plus depressive symptoms and medications <sup>§</sup>	10.4	5.5, 15.4	<0.001
Adjusted for the above plus total reversibility severity score with conventional stress	10.2	5.3, 15.1	<0.001
Myocardial Ischemia (Visual Analysis)			
	Odds Ratio for Ischemia in Women Versus Men Per 10-Year Decrement in Age	95% CI	P for Sex by Age Interaction
Adjusted for sociodemographic and lifestyle factors <sup>†</sup>	2.06	1.22, 3.49	0.007
Adjusted for the above plus CHD risk factors, other medical history and CAD severity <sup>‡</sup>	2.09	1.21, 3.61	0.008
Adjusted for the above plus depressive symptoms and medications <sup>§</sup>	2.17	1.25, 3.79	0.006
Adjusted for the above plus myocardial ischemia with conventional stress	2.06	1.12, 3.79	0.02

CAD indicates coronary artery disease; CHD, coronary heart disease.

\*Age was included as a continuous variable. The effects shown were calculated from the interaction between sex and age in each model. Covariables were added sequentially, so that later models contain all the variables included in earlier models.

<sup>†</sup>Race (black vs nonblack), years of education, income below poverty level ( $\leq$ \$20 000), current smoking, and body mass index.

<sup>‡</sup>History of myocardial infarction, heart failure, hypertension, dyslipidemia, diabetes mellitus, previous revascularization, resting left ventricular ejection fraction, and Gensini angiographic score.

<sup>§</sup>Beck Depression Inventory score, and use of beta-blockers, angiotensin-converting enzyme Inhibitors, antidepressants, and anxiolytics.

study, we found that women  $\leq$ 50 years with a recent MI had a similar inflammatory response to stress than men, but the level of interleukin-6 was 2 times higher in women than men before, during, and after the stress challenge.<sup>34</sup> It is possible that the high absolute levels of inflammation reached during stressful events pose young women above a threshold of risk for abnormal emotional and vascular responses to stress.

Most women  $\leq$ 50 years in our sample were premenopausal, whereas virtually all older women reported having reached menopause. Therefore, ovarian hormones may be implicated in our findings. Indeed, brain regions involved in the processing of emotional stimuli, such as the amygdala, hippocampus, and prefrontal cortex, are sensitive to changes in the hormonal

milieu, such as during the menstrual cycle, a process that may be affected by early-life stress exposure.<sup>35,36</sup> These same brain areas have direct or indirect outputs to neurohormonal systems involved in the stress response that, in turn, may affect vascular function and MSIMI. Furthermore, ovarian hormones may be the basis for the higher levels of inflammatory biomarkers that young women show compared to similarly aged men starting at age 16 in the community<sup>37</sup> and among MI patients.<sup>34</sup> This higher baseline inflammation may affect women's vascular responses to stress, as discussed above. These areas require further study.

More-severe disease in women with premature CHD is not a likely explanation for our findings. In this study, as in our

previous work,<sup>13</sup> women showed similar or less-pronounced CAD severity indicators than men and a similar level of traditional CHD risk factors except for diabetes mellitus. In addition, there were no significant sex differences in ischemia provoked by a conventional stress test. What may be at play, however, is a propensity toward microvascular dysfunction.<sup>38</sup> According to a prevailing model, MSIMI results primarily from insufficient dilation and/or constriction of the coronary microcirculation during stress.<sup>39</sup> Coronary microvascular dysfunction is common in women in the setting of chest pain without significant coronary obstruction,<sup>40,41</sup> and young women show more endothelial dysfunction than men in response to mental stress.<sup>42</sup> Furthermore, emotional stress and mood disturbances in daily life, which are more common in women and have been linked to ambulatory ischemia and MSIMI,<sup>43–45</sup> may lead to a chronic form of microvascular diastolic dysfunction.<sup>46</sup> Cumulative stress-induced sympathetic nervous system activation may be implicated, as suggested by the fact that patients with CHD who develop MSIMI have increased peripheral vasoconstriction.<sup>17</sup> These vascular effects may be accentuated in young women with CHD, given their higher baseline levels of inflammation.<sup>34</sup>

Our results are in tune with a recent statement from the American Heart Association highlighting the importance of stressful exposures and mood disorders as predisposing factors for premature CHD in young populations.<sup>47</sup> According to emerging data, young women may be especially vulnerable.<sup>7–9</sup> Given that MSIMI is associated with higher mortality in patients with CHD,<sup>16</sup> it could represent an important mechanism of risk and a novel prognostic indicator for young women with CHD. Because MSIMI correlates with myocardial ischemia and angina in daily life,<sup>15,48</sup> it may contribute to the triggering of acute coronary syndromes in young women and may play a role in their higher mortality post-MI compared to men.<sup>1</sup>

A limitation of our study is the relatively small number of young women, especially those below age 50 years; yet, this remains the largest investigation ever conducted of MSIMI in women. The extent of inducible ischemia with mental stress was overall relatively mild; however, women  $\leq 50$  years had on average around 3% of their myocardium with inducible ischemia with mental stress, a level that has clinical significance.<sup>21,22</sup> Furthermore, one third of these young women were classified as having ischemia according to accepted clinical criteria. Nonetheless, future outcomes studies are needed to confirm the clinical significance of MSIMI in women, given that previous studies have primarily included men.<sup>16</sup> Only 1 stress task is feasible with [<sup>99m</sup>Tc] sestamibi SPECT perfusion imaging, and this could be seen as an additional limitation. However, multiple mental stress tasks with short resting periods in between may not be more informative than just 1 task, because of possible carryover effects from one condition to the next.<sup>49,50</sup> The use of

myocardial perfusion imaging is a strength of our study, because it remains the gold standard for ischemia assessment. Furthermore, a major advantage of this technique for mental stress testing is that the radioisotope, once injected during mental stress, is trapped in the myocyte, providing a “snapshot” of perfusion at the time of stress.

## Conclusion

Among patients with CHD, we found significant differences in susceptibility to myocardial ischemia triggered by emotional stress according to sex and age, with young women showing more evidence of MSIMI. Future investigations should examine the role of MSIMI in the prognosis and etiology of CHD in women. These data may inform interventions specifically designed to address women’s stressors and reduce their burden of ischemic heart disease.

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