Published in final edited form as:

Circulation. 2018 February 20; 137(8): 794–805. doi:10.1161/CIRCULATIONAHA.117.030849.

Mental Stress Induced-Myocardial Ischemia in Young Patients with Recent Myocardial Infarction: Sex Differences and Mechanisms

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Abstract

Background—Mental stress-induced myocardial ischemia (MSIMI) is frequent in patients with coronary artery disease (CAD) and is associated with worse prognosis. Young women with a previous myocardial infarction (MI), a group with unexplained higher mortality than men of comparable age, have shown elevated rates of MSIMI, but the mechanisms are unknown.

Methods—We studied 306 patients (150 women and 156 men) ≤61 years of age who were hospitalized for MI in the previous 8 months and 112 community controls (58 women and 54 men) frequency matched for sex and age to the MI patients. Endothelium-dependent flow-mediated

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Conflict of Interest Disclosures: Ernest V. Garcia receives royalties from the sale of the Emory Cardiac Toolbox, used for some analyses in this study. None of the other authors report conflict of interest relevant to this article. The sponsors of this study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

dilation (FMD) and microvascular reactivity [reactive hyperemia index (RHI)] were measured at rest and 30-min after mental stress. The digital vasomotor response to mental stress was assessed using peripheral arterial tonometry (PAT). Patients received ^{99m}Tc-sestamibi myocardial perfusion imaging at rest, with mental (speech task) and with conventional (exercise/pharmacological) stress.

Results—The mean age of the sample was 50 years (range, 22–61). In the MI group, but not among controls, women had a more adverse socioeconomic and psychosocial profile than men. There were no sex differences in cardiovascular risk factors, and among MI patients clinical severity tended to be lower in women. Women in both groups showed a higher PAT ratio during mental stress but a lower RHI post-mental stress, indicating enhanced post-stress microvascular dysfunction. There were no sex differences in FMD changes with mental stress. The rate of MSIMI was twice as high in women as in men (22% vs 11%, p=0.009), and ischemia with conventional stress was similarly elevated (31% vs 16%, p=0.002). Psychosocial and clinical risk factors did not explain sex differences in inducible ischemia. While vascular responses to mental stress (PAT ratio and RHI) also did not explain sex differences in MSIMI, they were predictive of MSIMI in women only.

Conclusions—Young women post-MI have a two-fold likelihood of developing MSIMI compared with men, and a similar increase in conventional stress ischemia. Microvascular dysfunction and peripheral vasoconstriction with mental stress are implicated in MSIMI among women but not among men, perhaps reflecting women's proclivity towards ischemia due to microcirculatory abnormalities.

Keywords

sex; ischemia; stress; vascular function; microcirculation

INTRODUCTION

Women with early-onset myocardial infarction (MI) have received growing attention as a group affected by unexplained inequalities in health outcomes.[1] Young and middle-aged women with MI have poorer morbidity, mortality and quality of life relative to otherwise comparable men, which are unexplained by traditional risk factors, comorbidities, treatments, and MI severity indicators. There is concern that alternative risk factors relevant for women may be unrecognized, and psychosocial factors may be especially important in this context.[2, 3]

Depression, trauma, and perceived stress are disproportionally common in younger post-MI women as compared with their male counterparts or older patients,[4–7] and are powerful predictors of cardiovascular risk in young women.[8–12] Yet the psychosocial domain has rarely been evaluated in the context of sex-related cardiovascular health inequalities in post-MI patients. Recently, we have proposed a dominant role for the psychosocial sphere on cardiovascular risk and outcome in young women with early onset ischemic heart disease.[13, 14] However, objective evidence of this vulnerability is still insufficient.

Mental stress-induced myocardial ischemia (MSIMI) is a frequent phenomenon in patients with coronary artery disease (CAD) and is associated with a doubling of recurrent events and mortality, to a similar extent as ischemia provoked by a conventional stress test.[15] However, in contrast to conventional stress-induced ischemia, MSIMI is thought to reflect a dysregulated response to emotional stress rather than underlying CAD severity. Thus, there is growing interest in MSIMI as a marker of cardiovascular vulnerability to emotional stress.[16, 17] We have previously reported, in a small sample, that young women with a recent MI had twice the rate of MSIMI than male counterparts.[4] These findings were replicated in a broader sample of patients with stable CAD.[18] We have also shown that for women, but not for men, stress-induced peripheral vasoconstriction with mental stress is a dominant mechanism of MSIMI, perhaps reflecting women's proclivity towards microvascular dysfunction.[19] These previous studies, however, were limited by a small number of younger women, which precluded an investigation of whether differential vascular responses to mental stress explained sex differences in MSIMI.

In the current study of young post-MI patients, we sought to confirm that women have a higher propensity for MSIMI than men, and to empirically assess underlying vascular determinants of these differences. Furthermore, in order to provide a more in-depth understanding of potential sex-related behavioral and vascular factors implicated in cardiovascular disease, we examined sex differences in psychosocial characteristics and vascular stress responses in a sample of healthy community controls matched to the MI cases.

METHODS

Study Sample and Design

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study participants for the Myocardial Infarction and Mental stress 2 (MIMS2) study included early-onset MI cases and community controls without a history of CAD. The MI cases were recruited from the pool of patients who were admitted with a documented history of MI in the previous 8 months at Emory-affiliated hospitals in Atlanta, Georgia, and who were 18 to 60 years of age at the time of screening. The diagnosis of MI (Type 1) was verified by medical record review based on standard criteria of troponin level increase together with symptoms of ischemia and/or ECG changes or other evidence of myocardial necrosis; presence of obstructive CAD was not a criterion for inclusion.[20] Controls were recruited in the Atlanta area from a community-based study of individuals without established CAD.[21] Inclusion criteria for controls were aged between 18 and 60, and no past history of MI, unstable or stable angina pectoris, congestive heart failure, or stroke. Controls were frequency matched for age and sex to the MI cases, with the goal of achieving approximately 50% women and a similar mean age in both samples.

Subjects were excluded if they had a severe comorbid medical or psychiatric disorder that could interfere with study results, such as cancer, renal failure, severe uncontrolled hypertension, current alcohol or substance abuse or schizophrenia, if they were pregnant or

breastfeeding, or if they were currently using immunosuppressant or psychotropic medications other than antidepressants. MI patients were also excluded if they had unstable angina, acute MI or decompensated heart failure within the past week; if they weighed over 450 lbs (due to limits on the weight bearing of the nuclear stress test equipment); and if it was deemed to be unsafe by study cardiologists to hold anti-ischemic medications for 24 hours before the testing.

Both MI cases and healthy controls underwent a standardized mental stress test and vascular testing as described below and following published methodology.[22] The MI patients, but not the controls, also underwent single-photon emission computed tomography (SPECT) imaging studies with mental stress and with exercise or pharmacological stress. Sociodemographic and psychosocial data were collected for all participants prior to all testing. At the end of the study protocol, medical records for the MI patients were abstracted for clinical information, including catheterization data. The Emory University Institutional Review Board approved the protocol and all participants provided written informed consent.

Mental Stress Procedure

After resting for 30 minutes in a quiet, dimly lit, temperature-controlled room, mental stress was induced in both MI patients and controls by a standardized public speaking task as previously described.[4, 18, 22] Participants 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 two minutes to prepare a statement and then three minutes to present it in front of a video camera and an audience wearing white coats. Subjects were told that their speech would be evaluated by the laboratory staff for content, quality and duration. We recorded blood pressure and heart rate at five-minute intervals during the resting phase and at one-minute intervals during the mental stress task, and calculated the rate-pressure product as peak systolic blood pressure times peak heart rate. We also obtained subjective ratings of distress with the Subjective Units of Distress Scale [23] on a linear scale of 0 to 100, with 100 being the highest level of distress.

Vascular Testing

Among both MI patients and controls, we assessed peripheral vasoconstriction and microvascular function using the Endo-PAT2000 (Itamar Medical, Caesarea, Israel), which measures finger pulse volume amplitude (PVA), reflecting peripheral blood volume changes using volume plethysmography technology.[24, 25] PVA signals detected by a finger probe were filtered, amplified, and analyzed in an operator-independent manner. The baseline PVA was determined by averaging the last 3 minutes of recording that preceded the mental stress test. The stress amplitude was determined as the lowest PVA during the speaking period. The peripheral arterial tonometry (PAT) ratio was then calculated by the software as the ratio of PVA during the speaking task over the resting baseline, with a ratio <1 signifying a vasoconstrictive response. After removing participants with excessive artifacts, the PAT ratio was available in 76% of MI cases and 72% of controls.

Before and 30 minutes after the mental stress test we also used the EndoPAT device to assess the digital reactive hyperemia index (RHI), a measurement of peripheral microvascular

function. For this test, PVA is obtained in resting condition and during reactive hyperemia, which is elicited by the release of an upper arm blood pressure cuff inflated to suprasystolic pressure for 5 minutes. The RHI is then calculated as the ratio of post-deflation to baseline pulse amplitude in the hyperemic finger divided by the ratio in the contra-lateral finger.[26] This metric is calculated by a computer algorithm and has been associated with cardiovascular outcomes.[27] Before and 30 minutes after the mental stress test MI patients and controls also underwent measurement of flow-mediated vasodilation (FMD) of the brachial artery via bi-mode ultrasound to assess endothelial function using standard methodology.[28]

Myocardial Perfusion Imaging

MI subjects underwent three SPECT myocardial perfusion imaging scans following injection of sestamibi radiolabeled with Technetium-99m ([^{99m}Tc]), at rest, during mental stress, and during conventional stress, at the dose of 10–14 mCi of ^{99m}Tc for rest imaging and 30–40 mCi for stress imaging, based on weight. Testing was done in two separate days up to one week apart on a dedicated SPECT camera (Philips Cardio MD) without attenuation correction. We withheld anti-ischemic medications for 24 hours prior to testing following standard nuclear cardiology protocols. On the mental stress day, [^{99m}Tc]sestamibi was injected one minute after the onset of the public speech task. On the conventional stress day, subjects underwent a standard Bruce protocol, or (if unable to exercise) a pharmacological stress test with regadenoson (Abbott, Chicago, IL). The radioisotope injection was given at peak exertion or immediately after the regadenoson injection.

An experienced nuclear cardiologist (PR) performed visual interpretation blinded to stress test type and clinical data. 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 calculated summed scores in a conventional fashion, including a summed stress score (SSS), a summed rest score (SRS), and a summed difference score (SDS).[29] For exercise and pharmacological stress, presence of ischemia was defined as a SDS ≥4.[30] A SDS ≥3 is typically used as evidence of MSIMI.[31] To check the robustness of the results, we also calculated percent ischemic myocardium as (SDS/68) × 100 as a semiquantitative measure of inducible ischemia for both conditions. Moreover, we computed the number of ischemic segments as an additional measure of ischemic burden. Within each segment, we defined myocardial ischemia as a new perfusion abnormality (a score of ≥2), or worsening of pre-existing abnormality by at least 2 points in a single segment, or by at least 1 point in two or more contiguous segments.

Other Measurements

A research nurse obtained detailed sociodemographic, medical history and medication information, and measured weight and height to calculate the BMI. Trained personnel abstracted medical records for the index MI including clinical and angiographic data. Obstructive CAD was defined as ≥ 70% 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.[32]

We used validated instruments to assess behavioral, social, and health status information for both MI patients and controls. Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II),[33] a reliable and valid self-report measure which has been widely used in cardiac as well as non-cardiac populations. In addition, we administered the Structured Clinical Interview for DSM IV (SCID)[34] to derive a lifetime diagnosis of major depression and posttraumatic stress disorder (PTSD). The SCID was administered by a trained research nurse under the supervision of the study psychiatrist (JDB), who reviewed psychiatric diagnoses. We also administered the Cohen's Perceived Stress Scale,[35] a 10-item survey of general stress validated in multi-ethnic populations, and the Spielberger's State-Trait Anxiety Inventory, a 40-item questionnaire to measure anxiety as an emotional state or a personality trait.[36]

Statistical Analysis

We compared women and men within each group (MI patients and controls) for demographic, behavioral and clinical characteristics, as well as for hemodynamic and vascular changes during mental stress (and, among MI subjects, conventional stress), using t tests for continuous variables and chi-squared tests for categorical variables. Similar testing was done to compare MI patients with controls; furthermore, we tested for sex by group interactions using mixed regression models for continuous variables and Breslow-Day tests for categorical variables. Since the distribution of the PAT ratio was highly skewed, it was log transformed in the analysis, and results were presented as geometric means.

For the MI group, we fitted logistic models to assess sex differences in ischemia as a binary variable for both mental stress and conventional stress. Using nested models, we sequentially adjusted for sociodemographic and lifestyle characteristics, clinical risk variables and CAD severity indicators, and, lastly, psychosocial factors. In a final model, we evaluated whether the results were independent of presence of ischemia with the alternative stress modality.

To assess potential vascular mechanisms for sex differences in MSIMI, we included resting hemodynamics and vascular function measures, and their change with mental stress, to a model with MSIMI as a dependent variable. Additionally, we evaluated whether women and men differed in hemodynamic and vascular predictors of MSIMI, by constructing sex-stratified models and testing interactions by sex. For these analyses, we only considered measures obtained either at rest or during the stress procedure. Measurements of vascular function obtained 30 minutes after stress (FMD and RHI) were not considered relevant for this analysis. All these models were adjusted for body surface area and CAD severity indicators, including Gensini CAD severity score and resting perfusion defect severity (summed rest score).

Missing data were minimal or absent except for angiographic data, which were missing in 7% of the sample, and vascular function data, which were missing between 5% and 25% of the sample, depending on the variable. To avoid loss of information and possible bias due to missing covariate values, we performed multiple imputations for statistical models that included angiographic or vascular function data. Data were imputed 50 times using the Markov chain Monte Carlo method of multiple imputation, implemented using SAS PROC MI, and imputed regression estimates were combined via SAS PROC MIANYLYZE.[37] We

also assessed the missing at random (MAR) assumption by differential weighting of variable values (SAS MNAR statement) and found results to be nearly identical, thus justifying reliance on the MAR assumption. The estimates in the imputed analysis matched very closely the not-imputed results, suggesting that bias was minimal or absent. Nonetheless, we report results based on imputed datasets for models that included angiographic or vascular function data. All analyses were conducted using SAS statistical software version 9.4 (SAS Inc., Cary, NC).

RESULTS

Study Sample and Baseline Characteristics

Between August 2012 and March 2016, we enrolled 313 MI cases and 112 controls in the MIMS2 study. We excluded 7 MI cases with missing nuclear imaging results, leaving 306 MI subjects (150 women and 156 men) and 112 controls (58 women and 54 men) in the analytical sample. The mean age was 50.5 years overall, and it was 50.8 years in the MI group (range, 25 to 61 years) and 49.5 in the control group (range, 22 to 61 years). All subjects were younger than 61 years, except for three whose birthday occurred after screening but before study visits. The mean and median time from the date of the index MI to the study visit was 5 months for both women and men.

Compared to men with MI, women with MI had a more adverse sociodemographic and psychosocial profile, including lower income and education and higher levels of depression, PTSD, and perceived stress, although there were no differences in anxiety (Table 1). Women with MI were also more likely to be Black/African American than men with MI. No such differences were found among controls. In both cases and controls, there were no sex differences in most cardiovascular risk factors and medications, except that women with MI were more likely to be diabetic than men with MI and women in both groups were more often taking antidepressants. When compared with their MI counterparts, both female and male controls had a better psychosocial risk profile, including higher income and education, lower rates of depression and PTSD, and lower symptoms of perceived stress and anxiety (all $p < 0.01$). Controls also exhibited a more favorable cardiovascular risk profile than MI patients, including lower levels of BMI, smoking, dyslipidemia, diabetes, and resting blood pressure (all $p<0.01$). This was true for both women and men, with no significant sex-by group interactions. Women in the control group were also more likely to self-describe themselves as premenopausal than women with MI (35% vs 23%, $p=0.08$).

Despite similarities in CAD risk factors, women with MI had less severe obstructive CAD than men, as evidenced by a lower Gensini score, a lower frequency of three-vessel disease, and a lower summed rest score, a measure of severity of fixed perfusion defects. Women also had a higher left ventricular ejection fraction. There were no sex differences in the proportions of ST-segment elevation MI, history of congestive heart failure, and previous revascularization.

A comparison of resting hemodynamics and vascular function between women and men with MI showed that women had a higher resting systolic blood pressure and heart rate, but vascular parameters (FMD and RHI) were similar at rest (Table 1). There were no sex

differences in any of the resting hemodynamic and vascular parameters among controls. As expected, both female and male controls had a more preserved vascular function than their MI counterparts.

Hemodynamic, Vascular and Subjective Responses to Stress

Overall, hemodynamic responses to mental stress were similar in MI cases and controls, except for a blunted heart rate response among patients. Women in both groups exhibited a slightly higher rate pressure product with mental stress than their male counterparts (Table 2). Furthermore, women in both groups showed a lower RHI post-mental stress and a larger post-stress RHI decline compared with men, indicating enhanced microvascular dysfunction with mental stress. In contrast, there were no sex differences in either group in FMD changes with mental stress. In both groups the PAT ratio was higher in women than men (denoting less vasoconstriction), but women with MI, and not men with MI, showed more enhanced vasoconstriction than their respective controls ($p=0.036$ for the interaction between group and sex). There were no sex differences in any of the hemodynamic and vascular responses to conventional stress.

Myocardial Perfusion

Overall, 50 (16%) MI subjects developed myocardial ischemia with mental stress, and 69 (23%) with conventional stress. Women showed two times more myocardial ischemia than men, with both mental stress and conventional stress (Table 3). This was true irrespective of whether ischemia was analyzed as a dichotomous variable (presence/absence of ischemia), as a quantitative score (percent of ischemic myocardium), or as a count of ischemic myocardial segments. Despite the similarity of results for ischemia with mental and conventional stress, the correlation between the two types of ischemia was modest (Spearman correlation coefficient=0.20, $p=0.002$), and of the 119 MI cases who developed ischemia with either condition, only 20 (17%) were positive for both mental stress and conventional stress ischemia. This proportion was similar in women (19%) and in men (12%).

Adjustment for sociodemographic and lifestyle factors, CAD severity, and psychosocial factors did not substantially affect sex differences in ischemia with either condition, and the alternative stress test result also did not explain MSIMI or CSIMI, even though they were mildly associated (Table 4).

Vascular Mechanisms for Sex Differences in MSIMI

To assess potential vascular mechanisms of sex differences in MSIMI, we examined whether resting hemodynamic and vascular measures, and their changes with mental stress, explained sex differences in MSIMI. These analyses were adjusted for body surface area and CAD severity (Gensini CAD severity score and SPECT summed rest score). After including resting RPP and resting RHI to the model, the odds ratio (OR) of MSIMI for women compared with men was 2.6 (95% CI, 1.3–5.4). Adding resting FMD to the model did not change the results (OR, 2.6; 95% CI, 1.3–5.3). Adjustment for change in RPP with mental stress (OR, 2.7; 95% CI, 1.3–5.4), and further adjustment for PAT ratio with mental stress (OR, 3.0; 95% CI, 1.5–6.4) also did not weaken the association between sex and MSIMI.

Of the hemodynamic and vascular measures evaluated in these models, only a lower PAT ratio, denoting greater vasoconstriction with mental stress, was significantly associated with MSIMI (p=0.01), while a lower resting RHI, denoting lower baseline microvascular function, was borderline (p=0.06). However, these results were driven by women, as a lower resting RHI and a lower PAT ratio were related to MSIMI in women only (Table 5). The interaction effect with sex was borderline significant for PAT ratio (p=0.058). There was no significant association between rate pressure product (either the resting value or the change with mental stress) and MSIMI, in either women or men. None of these vascular measurements were associated with ischemia with conventional stress (data not shown).

DISCUSSION

We found that young and middle-aged women with a recent MI had a doubling of the odds of developing MSIMI compared with men, and they also showed a similar increase in ischemia induced by conventional stress. This was observed despite the fact that women had less obstructive CAD than men. Of several hemodynamic and vascular measures, a lower PAT ratio, indicator of peripheral vasoconstriction with mental stress, and a lower resting RHI, a marker of baseline microvascular dysfunction, were associated with MSIMI, suggesting the importance of sympathetically mediated vasomotor effects in the pathogenesis of MSIMI. While these vascular responses did not explain sex differences in MSIMI, they were predictive of MSIMI in women only, supporting women's vulnerability towards the effects of the microcirculation on myocardial ischemia. Our data corroborate a large literature suggesting the importance of microvascular dysfunction in the etiology of ischemic heart disease in women,[38] and suggest that this mechanism may be at play in determining a higher rate of MSIMI among women.[16]

Our results are in line with previous reports of higher rates of MSIMI in women, especially younger women, compared with men of comparable age and clinical characteristics.[4, 18, 39] Using a similar protocol in a small study of post-MI patients, we previously reported similar findings of a higher rate of MSIMI in women.[4] In a larger sample of patients with broadly defined stable CAD, we also previously described a sex by age interaction such that the vulnerability towards MSIMI applies to younger women only.[18] Other studies have reported mixed results concerning sex differences in MSIMI, but they predominantly enrolled older patients.[39, 40]

A major objective of the current study was to explore potential mechanisms of sex differences in MSIMI. Since psychosocial status and vascular function are profoundly affected by presence of CAD, we also studied matched healthy community controls. In the MI group, women compared with men had a larger burden of socioeconomic and emotional risk factors, including lower income and education, and higher levels of psychosocial distress (symptoms of depression, PTSD, and perceived stress). The fact that no such differences were found in community controls, suggests that these factors may be more often implicated in the risk of early-onset MI among women than men, or may occur as a consequence of the MI in women more often than in men. However, these factors did not explain the higher odds of MSIMI in women compared with men, suggesting that other factors, alone or in combination, must be at play.

Severity of CAD is unlikely to be implicated in the sex differences in MSIMI. Consistent with previous studies,[1, 4, 18] we found that women with MI had actually less severe CAD than their male counterparts, and vascular function at baseline was similar in women and men in both patients and controls. However, after mental stress, women compared with men exhibited a more pronounced decline in RHI, an indicator of decreased peripheral microvascular flow during reactive hyperemia testing, a difference that was observed in both patients and controls. Thus, psychological stress may elicit a more adverse microvascular response among women even though resting values are similar. The involvement of the microvascular circulation is suggested by the fact that there were no sex differences in FMD changes (an indicator of macrovascular endothelial dysfunction) with mental stress in either patients or controls. Furthermore, the PAT ratio, which mostly reflects vasoconstriction of larger peripheral vessels during stress, was actually higher in women than in men, as previous studies also reported.[41] Additionally, the fact that both women patients and women controls, but not men in either group, exhibited a lower post-stress microcirculatory function (denoted by a lower RHI) suggests that microvascular responses to stress could be an important element of sex differences in cardiovascular disease etiology. These results also point to the importance of studying dynamic changes in vascular function with pertinent exposures in order to fully understand sex differences in cardiovascular pathophysiology.

In addition to sex differences in vascular responses with mental stress, our data suggest that women are more susceptible than men to the effects of vasomotion and microvascular function as substrates of MSIMI. In fact, peripheral vasoconstriction with mental stress (PAT ratio) and baseline microvascular function (RHI) were predictive of MSIMI in women only. These data parallel our findings in a separate sample of CAD patients, where PAT ratio was predictive of MSIMI in women but not in men.[19] In that study, however, we also found that in men MSIMI was predicted by increased hemodynamic stress reactivity, which was not the case in the present study. This apparent discrepancy may be due to differences in study populations, which in our previous study included predominantly older patients with broadly defined CAD.

As a whole, our results suggest that the higher rate of MSIMI in women could be due to women's vulnerability to ischemia secondary to microvascular dysfunction or to sympathetically mediated vascular reactivity. Our data corroborate a prevailing model that MSIMI results primarily from insufficient dilation and or enhanced constriction of the coronary microcirculation during stress, rather than from obstructive CAD.[42] This model of microcirculatory dysfunction in MSIMI could be especially applicable to women, and fits current hypotheses of ischemic heart disease pathophysiology in this group.[16]

We found that women were also more likely than men to develop ischemia with a conventional stress test. These results were unexpected, since women had less severe CAD than men, and other studies have reported a lower incidence of ischemia in women than in men after an MI,[43] or a similar extent of ischemia despite less prevalent angiographic CAD.[44] However, these previous studies primarily included older patients. In a separate report, we found a similar tendency for young women with CAD to show more ischemia than men of comparable age.[18] Therefore, it is possible that young women with CAD, and especially those who have recently survived an MI, are disproportionately prone to myocardial

ischemia; the mechanisms for this sex difference deserve further study. In our investigation, there was little overlap between MSIMI and conventional stress ischemia, and the latter was not predicted by microvascular function at rest or vasoconstrictive responses with mental stress in either women or men, suggesting that these are, for the most part, separate phenomena.

Our findings have substantial implications. Despite considerable progress in improving the awareness of cardiovascular disease as a major cause of morbidity and mortality in women, there seems to be stagnation towards a reduction in MI incidence and mortality among younger women in comparison with other groups.[45–48] Hospitalization rates for MI are increasing disproportionately in women younger than 65 years,[45–47, 49] and overall heart disease mortality rates are declining less in this group than other segments of the United States population.[50] While recent adverse trends in obesity and smoking may be implicated, traditional risk factors do not explain these disparities.[3] There is concern that a lack of acknowledgment of alternative, unmeasured risk factors relevant to women may undermine primary and secondary prevention efforts for young women.[2, 3] In this context, the high rate of MSIMI and of myocardial ischemia in general we describe in this group, together with their adverse psychosocial profile, provide new potential avenues for risk assessment and prevention for women.

Our study has limitations worth noting. The extent of inducible ischemia with mental stress was overall relatively mild, and because we lacked outcome data, the clinical significance of our findings need further study. Although the prognostic significance of MSIMI has been established, previous studies have predominantly included men,[15] and thus more data are warranted regarding the clinical significance of MSIMI in women. It is possible that the speech task we used for mental stress testing, while an established method in studies where ischemia is assessed with [^{99m}Tc]sestamibi perfusion imaging, may have limited sensitivity or specificity for the assessment of acute stress in this population. However, if this were an issue, it would bias the estimates towards the null. Finally, our study was conducted at a single institution and generalizability to other populations and settings also need further investigation. Despite these limitations, this remains the largest and possibly the only study of MSIMI in young post-MI patients. The experimental design, the inclusion of community controls, and the large number of women and minorities are unique strengths of our investigation. Finally, we used myocardial perfusion imaging, which remains the gold standard for ischemia assessment and has important advantages for mental stress testing, since the radioisotope is injected during mental stress and provides a “snapshot” of perfusion at the time of stress.

In conclusion, young and middle-aged women with a recent MI have a two-fold likelihood of developing MSIMI compared with men, and a similar increase in ischemia induced by a conventional stress test. Furthermore, microvascular dysfunction and stress-induced peripheral vasoconstriction are implicated in MSIMI for women but not for men, perhaps reflecting women’s proclivity towards ischemia due to microcirculatory abnormalities.

Acknowledgments

Funding Sources: This work was supported by the NIH, through the following grants: R01 HL109413, R01HL109413-02S1, R01 HL125246, R01 HL136205, P01 HL101398, KL2TR000455, K24HL077506, K24 MH076955, K23HL127251, and THL130025A.

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Clinical Perspective

What is new?

- Previous research has suggested elevated rates of myocardial ischemia provoked by mental stress in young women with coronary artery disease, but data remain limited and the mechanisms are unclear.
- We found that young women who have survived a recent myocardial infarction (MI) have a two-fold likelihood of developing ischemia with mental stress compared with men of similar age.
- Furthermore, we found that microvascular dysfunction and peripheral vasoconstriction during mental stress were related to mental stress-induced ischemia among women, but not among men.

What are the clinical implications?

- Younger women with MI, compared with men of similar age, are known to have unexplained adverse outcomes in terms of morbidity, mortality and quality of life.
- Stressful exposures may play an important role in this group, by inducing myocardial ischemia through sympathetically mediated effects on the microcirculation.
- Our results should inform future efforts aimed at improving risk assessment and secondary prevention for women with early-onset MI, where adequate consideration is given to the psychosocial sphere.

Circulation. Author manuscript; available in PMC 2019 February 20.

Table 1

Characteristics of the study population by sex.

	MI Patients			Controls		
	Women> N=150	**Men N=156**	**p**	**Women N=58**	**Men N=54**	**p**
Demographic Factors						
Age, years, mean (SD)	50 (7)	51 (6)	0.4	51 (8)	48 (10)	0.2
Black/African American, %	75	57	0.001	48	37	0.2
Married or living with partner, %	36	48	0.03	52	56	0.7
Income ≤ $25,000, %	48	34	0.01	7	14	0.2
Years of education, mean (SD)	13(3)	14 (3)	0.07	16(2)	17(3)	0.4
Premenopausal, %	23	--	--	35	--	--
Psychosocial Risk Factors						
Lifetime history of major depression, %	45	28	0.002	19	20	0.8
Current major depression, %	21	12	0.049	1.7	3.7	0.5
Beck Depression Inventory, mean (SD)	14 (11)	11 (10)	0.004	6 (8)	6 (7)	0.7
Lifetime history of PTSD, %	18	11	0.1	3	6	0.6
Current PTSD, %	13	9	0.3	3.5	3.7	0.9
PTSD Symptom Checklist, mean (SD)	33 (15)	31 (15)	0.1	23 (10)	25 (12)	0.3
Perceived Stress Scale, mean (SD)	18 (8)	15 (8)	0.004	10 (6)	11 (6)	0.7
State Anxiety, mean (SD)	37 (13)	35 (13)	0.4	29 (9)	31 (10)	0.3
Trait Anxiety, mean (SD)	39 (11)	37 (13)	0.2	31 (9)	32 (10)	0.7
Cardiovascular Risk Factors						
BMI, kg/m^2, mean (SD)	33 (8)	30 (6)	0.003	29 (7)	29 (5)	0.9
Ever smoker, %	61	56	0.4	25	30	0.5
History of hypertension, %	83	78	0.3	33	28	0.6
History of dyslipidemia, %	79	82	0.5	34	28	0.4
History of diabetes, %	37	27	0.07	9	6	0.5
Medications						
Beta Blocker, %	85	85	0.9	5	6	0.9
Statins, %	84	85	0.8	12	17	0.5

	MI Patients			Controls		
	Women> N=150	Men N=156	p	Women N=58	Men N=54	p
Aspirin, %	83	80	0.5	7	13	0.3
ACE Inhibitors, %	43	51	0.2	10	15	0.5
Anti diabetics, %	34	22	0.02	7	7	0.9
Antidepressants, %	23	11	0.004	23	9	0.05
Clinical Characteristics (MI Patients Only)						
ST-segment elevation MI, %	27	33	0.2	--	--	--
Maximum troponin, mean (SD)	22 (47)	35 (53)	0.1	--	--	--
History of MI prior to index MI, %	21	20	0.7	--	--	--
History of congestive heart failure, %	11	9	0.6	--	--	--
History of coronary bypass surgery, %	20	21	0.8	--	--	--
History of percutaneous intervention, %	71	68	0.6	--	--	--
LV ejection fraction (%), mean (SD)	53 (11)	48 (12.5)	<0.001	--	--	--
Gensini CAD severity score, mean (SD)*†	17 (4)	25 (4.)	0.03	--	--	--
Obstructive CAD (stenosis ≥70%), %‡	82	87	0.2	--	--	--
Three-vessel disease (at ≥70%), %‡	9	18	0.04	--	--	--
SPECT summed rest score, mean (SD)	3 (6)	5 (7)	0.03	--	--	--
Resting Hemodynamics						
Systolic blood pressure, mmHg, mean (SD)	137 (24)	131 (19)	0.01	120 (14)	122 (13)	0.6
Diastolic blood pressure, mmHg, mean (SD)	84 (13)	83 (12)	0.3	75 (9)	78 (9)	0.7
Heart rate, beat/min, mean (SD)	66 (10)	63 (11)	0.006	63 (9)	61 (9)	0.1
RPP, beat × mmHg/min per 1,000, mean (SD)	7.7 (2.0)	7.1 (1.9)	0.007	6.7 (1.5)	6.4 (1.2)	0.4
Resting Vascular Function‡						
RHI, mean (SD)	1.7 (0.6)	1.8 (0.5)	0.1	1.8 (0.5)	1.9 (0.5)	0.6
FMD percent, mean (SD)	3.9 (2.8)	3.8 (2.7)	0.7	5.3 (2.2)	4.9 (3.0)	0.5

BDI: Beck Depression Inventory; BMI: Body mass index; MI: myocardial infarction; LV: left ventricle; CAD: coronary artery disease; SPECT: single-photon computed tomography; RPP: rate-pressure product; FMD: flow-mediated vasodilation; RHI: reactive hyperemia index.

*Geometric means.

†Angiographic data available in 286 patients (93%). There were no differences in missing data by sex.

‡Vascular data available in a minimum of 283 (92%) MI cases, and 106 (95%) controls. There were no differences in missing data by sex.

Table 2

Sex differences in hemodynamic, vascular and subjective responses to stress.

	MI Patients			Controls		
	Women N=150	**Men N=156**	**p**	**Women N=58**	**Men N=54**	**p**
Mental Stress						
Hemodynamic Responses*						
Systolic blood pressure, mm Hg, mean change (SD)	41 (17)	40 (16)	0.5	44 (15)	41 (16)	0.4
Diastolic blood pressure, mm Hg, mean change (SD)	28 (12)	28 (11)	0.9	29 (12)	25 (8)	0.05
Heart rate, beats/min, mean change (SD)	25 (16)	22 (13)	0.1	33 (15)	26 (13)	0.005
RPP, per 1,000, post-stress (SD)	14 (4)	13 (3)	0.002	15 (4)	13 (3)	0.01
RPP, per 1,000, mean change (SD)	7 (3)	6 (2)	0.02	8 (3)	6 (3)	0.01
Vascular Responses						
RHI, post-stress, mean (SD)	1.6 (0.6)	1.8 (0.6)	0.03	1.7 (0.6)	2.0 (0.5)	0.006
RHI,† mean change (SD)	−0.08 (0.54)	−0.02 (0.50)	0.3	−0.12 (0.52)	0.13 (0.58)	0.03
FMD percent, post-stress, mean (SD)	2.2 (2.2)	2.1 (2.4)	0.8	3.5 (1.9)	3.0 (2.2)	0.2
FMD percent,† mean change (SD)	−1.7 (2.1)	−1.7 (2.1)	0.9	−1.8 (1.4)	−1.9 (2.9)	0.7
PAT Ratio,‡ mean (SD)	0.72 (0.52)	0.62 (0.39)	0.049	0.88 (0.65)	0.56 (0.58)	0.001
Subjective Units of Distress Scale, mean changez (SD)	29 (35)	23 (25)	0.1	32 (28)	33 (27)	0.8
Conventional Stress (MI Patients Only)//						
Hemodynamic Responses						
Type of stress test (exercise vs pharmacological), %	65	75	0.07	--	--	--
Maximum heart rate, beats/min, mean (SD)	152 (12)	152 (12)	0.9	--	--	--
RPP, per 1,000, post-stress, mean (SD)	22.5 (6.1)	23.4 (5.9)	0.2	--	--	--
Percent max heart rate on treadmill, mean (SD)	88 (6)	88 (13)	0.7	--	--	--
Vascular Responses				--	--	--
RHI, post-stress, mean (SD)	1.7 (0.5)	1.8 (0.5)	0.2	--	--	--
RHI,† mean change (SD)	0.001 (0.6)	−0.05 (0.53)	0.4	--	--	--
FMD percent, post-stress, mean (SD)	2.9 (2.2)	2.5 (2.3)	0.2	--	--	--
FMD percent,† mean change (SD)	−1.0 (2.8)	−1.3 (2.5)	0.3	--	--	--

Values are all means (standard deviation), unless indicated otherwise.

SD: standard deviation; PAT: pulsatile arterial tonometry; RPP: rate-pressure product; FMD: flow-mediated vasodilation; RHI: reactive hyperemia index.

[*] Difference between maximum value during stress and minimum value during rest.

[†] Difference between posttest and pretest values: a negative value indicates worsened vascular function. Data available in a minimum of 282 (92%) MI cases and 105 (94%) controls for mental stress, and a minimum of 271 (89%) MI cases for conventional stress.

[‡] Ratio of pulse wave amplitude during the speaking task over the resting baseline, with lower values indicating greater vasoconstriction. The PAT ratio was log transformed and geometric means are presented here. Data were available in 234 (76%) MI cases and 80 (71%) controls. There were no differences in missing data by sex.

[§] Difference between posttest and pretest values: a positive value indicates higher distress with mental stress. Data available in 297 (97%) of MI cases and all controls.

[//] N=302 (4 patients did not receive a conventional stress test).

Table 3

Unadjusted sex differences in myocardial ischemia measures.

	Women		Men		P
Mental Stress (N=306)					
Myocardial Ischemia, n (%)	33	(22)	17	(11)	0.009
Number of ischemic segments, mean (95% CI)	0.6	(0.3, 0.9)	0.3	(0.1, 0.4)	0.03
% LV with Inducible Ischemia, n (%)					
0%	109	(73)	130	(83)	0.005†
>0% – <5%	16	(11)	16	(11)	
≥5% – <8%	13	(9)	6	(4)	
≥8%	12	(8)	4	(3)	
Conventional Stress (N=299) *					
Myocardial Ischemia, n (%)	45	(31)	24	(16)	0.002
Number of ischemic segments, mean (95% CI)	1.1	(0.7, 1.4)	0.6	(0.3, 0.8)	0.02
% LV with Inducible Ischemia, n (%)					
0%	88	(60)	113	(74)	0.002†
>0% – <5%	14	(9)	15	(10)	
≥5% – <8%	21	(14)	13	(9)	
≥8%	24	(16)	11	(7)	

LV: left ventricle. CI: confidence interval.

*7 patients had missing myocardial perfusion data with conventional stress.

†Mantel-Haenszel test for linear trend.

Table 4

Adjusted sex differences in myocardial ischemia with mental stress and conventional stress.

	Outcome: Myocardial Ischemia with Mental Stress Odds Ratio (95% CI) Women Vs. Men	Outcome: Myocardial Ischemia with Conventional Stress Odds Ratio (95% CI) Women Vs. Men
Adjusted for sociodemographic and lifestyle factors *	2.2 (1.1–4.3)	2.4 (1.3–4.2)
Adjusted for the above plus CAD risk factors, medical history and CAD severity †	3.0 (1.4–6.1)	3.0 (1.6–5.6)
Adjusted for the above plus psychosocial factors ‡ and antidepressant use	3.1 (1.5–6.6)	2.9 (1.5–5.5)
Adjusted for the above plus myocardial ischemia with alternative stress test	2.7 (1.3–5.9)	2.6 (1.4–5.0)

CI: confidence interval; CHD: CAD: coronary artery disease. The data shown are based on datasets where missing variable values were imputed.

*Age, race (black versus non-black), years of education, ever smoking and BMI.

†Hypertension, dyslipidemia, diabetes mellitus, ST-segment myocardial infarction, left ventricular ejection fraction, Gensini CAD severity score and resting perfusion defect severity (SPECT summed rest score).

‡Beck Depression Inventory score, PTSD Symptom Checklist score, and Perceived Stress Scale score. Substituting depression and PTSD symptom scores with DSM-IV diagnoses for depression and PTSD did not substantially change the results.

Table 5

Sex-specific association of hemodynamic and vascular function measures (at rest and during mental stress) with mental stress-induced myocardial ischemia.

	Outcome: Myocardial Ischemia with Mental Stress			
	Women Odds Ratio (95% CI)	*P*	Men Odds Ratio (95% CI)	*P*
Separate Models [*]				
Resting RPP, per 1,000 unit increment	0.98 (0.80 – 1.20)	0.9	0.91 (0.68 – 1.22)	0.5
RPP change with mental stress, per 1,000 unit increment [†]	1.04 (0.93 – 1.17)	0.5	1.17 (0.96 – 1.44)	0.1
Resting FMD absolute difference, per 0.10 mm decrement	1.12 (0.95 – 1.32)	0.2	0.87 (0.73 – 1.03)	0.1
Resting RHI, per 0.10 unit decrement	1.09 (1.00 – 1.19)	0.049	1.03 (0.93 – 1.13)	0.6
PAT ratio with mental stress, per 0.10 log unit decrement [‡]	1.12 (1.03 – 1.21)	0.01	1.03 (0.92 – 1.15)	0.5
Same Model [§]				
Resting RPP, per 1,000 unit increment	0.90 (0.72 – 1.13)	0.4	0.91 (0.68 – 1.22)	0.5
RPP change with mental stress, per 1,000 unit increment [†]	1.04 (0.92 – 1.19)	0.5	1.16 (0.95 – 1.42)	0.1
Resting RHI, per 0.10 unit decrement	1.14 (1.03 – 1.26)	0.009	1.03 (0.93 – 1.14)	0.6
PAT ratio with mental stress, per 0.10 log unit decrement [‡]	1.15 (1.04 –1.27)	0.004	1.03 (0.92 – 1.15)	0.6

PAT: pulsatile arterial tonometry; RPP: rate-pressure product; FMD: flow-mediated vasodilation; RHI: reactive hyperemia index. The data shown are based on datasets where missing variable values were imputed.

Variables in these models are those measured either at rest or during the stress procedure (with calculated change from baseline). Measurements done 30 minutes after stress (FMD post-stress and RHI post-stress) were not considered relevant for this analysis.

[*] Each measure listed was entered as independent variable in a separate model with MSIMI as dependent variable. All models adjusted for body surface area and severity of coronary artery disease (Gensini severity score and SPECT summed rest score).

[†] Difference between maximum value during stress and minimum value during rest.

[‡] Ratio of pulse wave amplitude during the speaking task over the resting baseline, with lower values indicating greater vasoconstriction. The PAT ratio was log transformed.

[§] All measures listed were included together as independent variables in a model with MSIMI as dependent variable. The model also adjusted for the same factors as above: body surface area and severity of coronary artery disease (Gensini severity score and SPECT summed rest score). Adding menopausal status to the model for women yielded similar results.