Sex Differences in Hemodynamic and Microvascular Mechanisms of Myocardial Ischemia Induced by Mental Stress

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Objective—To investigate sex-specific vascular mechanisms for mental stress-induced myocardial ischemia (MSIMI).

Approach and Results—Baseline data from a prospective cohort study of 678 patients with coronary artery disease underwent myocardial perfusion imaging before and during a public speaking stressor. The rate-pressure product response was calculated as the difference between the maximum value during the speech minus the minimum value during rest. Peripheral vasoconstriction by peripheral arterial tonometry was calculated as the ratio of pulse wave amplitude during the speech over the resting baseline; ratios <1 indicate a vasoconstrictive response. MSIMI was defined as percent of left ventricle that was ischemic and as a dichotomous variable. Men (but not women) with MSIMI had a higher rate-pressure product response than those without MSIMI (6500 versus 4800 mm Hg bpm), whereas women (but not men) with MSIMI had a significantly lower peripheral arterial tonometry ratio than those without MSIMI (0.5 versus 0.8). In adjusted linear regression, each 1000-U increase in rate-pressure product response was associated with 0.32% (95% confidence interval, 0.22–0.42) increase in inducible ischemia among men, whereas each 0.10-U decrease in peripheral arterial tonometry ratio was associated with 0.23% (95% confidence interval, 0.11–0.35) increase in inducible myocardial ischemia among women. Results were independent of conventional stress-induced myocardial ischemia.

Conclusions—Women and men have distinct cardiovascular reactivity mechanisms for MSIMI. For women, stress-induced peripheral vasoconstriction with mental stress, and not increased hemodynamic workload, is associated with MSIMI, whereas for men, it is the opposite. Future studies should examine these pathways on long-term outcomes.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2018;38: 473-480. DOI: 10.1161/ATVBAHA.117.309535.)**

Key Words: arteries ■ hemodynamics ■ humans ■ myocardial ischemia ■ vasoconstriction

Acute emotional stress and stress-induced physiological perturbations have long been observed to adversely affect cardiometabolic risk and predict future cardiovascular events.[1] Nonetheless, stress remains a relatively understudied and under-recognized risk factor.[2] Of recent growing interest is the effect of acute mental stress on inducible ischemia in patients with coronary artery disease (CAD).[3,4] Mental stress-induced myocardial ischemia (MSIMI) is associated with a 2-fold increased risk for adverse cardiac events and mortality, which is not explained by established cardiovascular risk factors or whether patients also have conventional (exercise or pharmacological) stress ischemia.[5,6] Recently, interest has grown in MSIMI as a metric that may index an individual's cardiovascular vulnerability to emotional stressors.[7]

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Emerging data suggest that women may be more vulnerable than men to the adverse effects of emotional stress on the cardiovascular system.[3,7] We and others have shown that women, and young women in particular, are more likely to develop MSIMI as compared with men and older patients.[8–10] The increased risk of MSIMI among women is not accounted for by severity of disease, traditional cardiovascular risk factors, or even behavioral or psychological risk factors, suggesting that alternative mechanisms may be important in understanding disparities in MSIMI.[8] Clarifying the mechanisms that may predispose women to MSIMI may help identify distinct physiological pathways for adverse long-term cardiovascular outcomes.

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Nonstandard Abbreviations and Acronyms	
BSA	body surface area
CAD	coronary artery disease
MIPS	mental stress ischemia mechanisms and prognosis study
MSIMI	mental stress-induced myocardial ischemia
PAT	peripheral arterial tonometry
RPP	rate-pressure product

Postulated mechanisms of MSIMI involve the well-known cardiovascular effects of sympathetic nervous system stimulation, including increased hemodynamic workload and enhanced vasoconstriction.[4,11–13] Stress-induced coronary vascular reactivity in the epicardial and microvascular circulation has been especially implicated in MSIMI.[4,12–15] Coronary microvascular dysfunction is characterized by a failure of resistance arterioles to dilate in response to myocardial demand or abnormal vasoconstriction to stimuli.[4,14,16] It is thought to be common in women, especially in the setting of nonobstructive epicardial CAD.[17] Thus, it is possible that stress-induced vasoconstriction is a predominant mechanism of MSIMI among women, although this question has not been directly assessed.

Recent evidence also links MSIMI to peripheral vasoconstriction measured directly during mental stress using peripheral arterial tonometry (PAT).[4,18,19] These data suggest that an increase in afterload caused by stress-induced peripheral microvascular resistance can affect the risk of MSIMI or, alternatively, that peripheral vasoconstriction is a proxy for a similar response occurring in the coronary circulation. Using PAT, we sought to investigate sex differences in the role that stress-induced peripheral microvascular reactivity plays in MSIMI and to contrast these results with those of stress-induced hemodynamic workload (blood pressure and heart rate). We hypothesized that in women, in contrast to men, vasoconstrictive responses to stress play a larger role than hemodynamic workload in predicting MSIMI.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement. Briefly, The MIPS (Mental Stress Ischemia Mechanisms and Prognosis Study) is a prospective study designed to investigate mechanisms and prognosis of MSIMI among patients with stable CAD. More detailed information on the MIPS objectives and study design has been described elsewhere.[9,20]

Results

Of the 678 participants included in the data set, 186 were women (Table 1). The mean age was 63 years in both women and men. Women and men had similar clinical and lifestyle risk profiles, but women were less likely to be white, and more likely to be poor, to have more depressive symptoms, angina during the past month, lower functional capacity, and to be taking antidepressants. CAD severity indicators (obstructive CAD with ≥50% stenosis, summed rest score, and Gensini score) were lower in women than in men, indicating less CAD plaque burden in women, but there were no sex differences in inducible ischemia. Only 5 women were currently taking postmenopausal hormones, whereas 34 indicated that they used postmenopausal hormones in the past. At rest, women had higher systolic blood pressure, higher heart rate, and higher rate-pressure product (RPP). In bivariate analyses, without adjusting for body surface area (BSA) or other covariates, there were no significant sex differences in RPP response during stress, whereas men had significantly lower PAT ratio (indicating greater vasoconstriction; Table 1).

Sex differences in hemodynamic workload throughout mental stress testing are shown in Figure 1. For ease of interpretation, MSIMI was dichotomized using accepted clinical criteria as described under Materials and Methods. All comparisons were adjusted for BSA—an important confounding factor for vascular parameters, given women's smaller body habitus. Compared with women without MSIMI, women who developed MSIMI had significantly higher heart rate throughout (at rest, during the speaking task, and recovery) but showed no significant differences in hemodynamic workload to stress, and the RPP did not differ. In contrast, men with MSIMI, compared with men without MSIMI, showed larger increases in all hemodynamic parameters during mental stress testing. When RPP response was examined as the difference between maximum value during stress and minimum value during rest, women and men had similar RPP responses overall (Figure 2A). However, when data were analyzed by MSIMI status (Figure 2B), men with MSIMI had significantly higher RPP response compared with men without MSIMI (6.5 versus 4.8) and women with MSIMI (6.5 versus 4.4), whereas there was no significant difference in RPP response between women with MSIMI and women without MSIMI (4.4 versus 4.8). Results remained virtually unchanged after adjusting for resting RPP.

A similar analysis for PAT provided opposite results. In the entire sample (Figure 2A), there was little difference in PAT ratio between women and men (0.8 versus 0.7) after adjusting for BSA. However, women with MSIMI had a significantly lower PAT ratio (denoting greater vasoconstriction) than women without MSIMI (0.5 versus 0.8) and men with MSIMI (0.5 versus 0.7), whereas there were no significant differences in PAT ratio for men by MSIMI status (0.7 versus 0.7; Figure 2B).

Linear regression models adjusted for BSA showed similar findings. The RPP response was significantly associated with a higher percent of ischemic left ventricular myocardium with mental stress only among men (Table 2). For each 1000-U increase in RPP response, there was a 0.28% increase in inducible ischemia for men (95% confidence interval, 0.19–0.38). The RPP response was not significantly associated with mental stress-induced ischemia among women, and there was a significant sex-by-RPP response interaction ($P<0.0001$). Results were similar after adjusting for demographic and clinical risk factors selected a priori, including age, race, history of diabetes mellitus, hypertension, previous myocardial infarction, subjective ratings of distress, β-blocker use, and resting RPP (model 2). We also tested whether additional factors might confound our results, including Gensini score, depression, antidepressant use, angina, and functional capacity, by comparing effect estimates from our main effects model (model 1) and a subsequent model that included each variable separately. However, because effect estimates did not change by >10% and our results were materially unchanged,

Table 1. Characteristics of Study Population by Sex

	Women	Men	
Total Number	186	492	*P* Value
Demographic factors			
Age, y, mean (SD)	62.6 (9.4)	63.0 (0.1)	0.65
White, n (%)	98 (52.7)	332 (67.5)	0.0004
Income below poverty status (≤$20 000), n (%)	43 (24.4)	63 (13.6)	0.001
Greater than high school education, n (%)	128 (71.1)	362 (74.6)	0.36
Clinical and lifestyle factors			
BMI, kg/m^2, mean (SD)	30.2 (6.1)	29.4 (4.9)	0.11
Smoking, n (%)	30 (16.1)	69 (14.1)	0.05
Depression (BDI≥10), n (%)	80 (44.4)	135 (28.4)	<0.0001
Diabetes mellitus, n (%)	71 (38.2)	151 (30.7)	0.06
Hypertension, n (%)	146 (78.5)	370 (75.2)	0.37
Dyslipidemia, n (%)	144 (77.4)	412 (83.7)	0.06
Myocardial infarction, n (%)	69 (37.1)	183 (37.2)	0.98
Heart failure, n (%)	29 (15.6)	67 (13.6)	0.51
Angina during past month, n (%)	78 (42.2)	118 (24.2)	<0.0001
Functional capacity, mean (SD)	33.5 (14.7)	43.6 (13.8)	<0.0001
Medications			
Aspirin, n (%)	156 (83.9)	428 (87.2)	0.27
β-Blocker, n (%)	143 (76.9)	361 (73.5)	0.37
ACE inhibitors, n (%)	65 (35.0)	245 (50.0)	0.001
Antidepressant, n (%)	60 (32.3)	94 (19.1)	0.0003
Statins, n (%)	154 (82.8)	422 (86.1)	0.28
Imaging data and CAD severity indicators			
Obstructive CAD (≥50% stenosis), n (%)	138 (86.3)	394 (92.3)	0.03
Previous revascularization, n (%)	145 (78.0)	377 (76.6)	0.71
Abnormal exercise or nuclear test, n (%)	38 (23.0)	102 (22.3)	0.84
Gensini score, mean (SD)	2.9 (1.4)	3.2 (1.3)	0.01
Summed rest score, mean (SD)	3.5 (7.1)	5.8 (9.3)	0.001
Percent LV with inducible mental stress ischemia, mean (SD)	1.3 (3.6)	1.1 (2.7)	0.34
Percent LV with inducible conventional stress ischemia, mean (SD)	3.3 (6.4)	3.9 (6.6)	0.33
Mental stress myocardial ischemia, n (%)	27 (14.2)	81 (16.5)	0.54
Conventional stress myocardial ischemia, n (%)	56 (31.3)	173 (36.1)	0.25
Resting hemodynamics			
SBP, mm Hg, mean (SD)	140.0 (20.5)	133.9 (16.6)	0.0003
DBP, mm Hg, mean (SD)	78.1 (10.6)	78.8 (10.2)	0.45
HR, bpm, mean (SD)	65.3 (11.3)	62.6 (10.8)	0.01
RPP, beats×mm Hg/min, mean (SD)	9141.7 (2110.9)	8400.0 (1850.1)	<0.0001
Response to stress			
Subjective units of distress, mean (SD)*	11.9 (24.3)	9.7 (13.7)	0.20
PAT ratio†	0.82 (0.43)	0.68 (0.30)	0.002
RPP response‡	5087.6 (2639.3)	4909.7 (2732.7)	0.45

ACE indicates angiotensin-converting enzyme; BDI, beck depression inventory; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HR, heart rate; LV, left ventricle; PAT, pulsatile arterial tonometry; RPP, rate-pressure product; and SBP, systolic blood pressure.

*Difference between post-test and pretest values. A positive value indicates higher distress with mental stress.

†The PAT ratio is calculated as the ratio of pulse wave amplitude during the speaking task over the resting baseline, with lower values indicating greater vasoconstriction.

‡RPP response is calculated as the difference between maximum value during stress and minimum value during rest.

these variables were not included in model 2. A final model added PAT ratio with mental stress and percent ischemia by conventional stress as adjustment factors, but results remained similar (model 3).

In contrast, PAT ratio was significantly associated with a higher percent of ischemic left ventricle with mental stress only among women (Table 2). For each 10-U decrease in PAT ratio, indicating greater vasoconstriction, there was a 0.23% increase in inducible ischemia for women (95% confidence interval, 0.11–0.35). The PAT ratio was not significantly associated with mental stress-induced ischemia among men (model 1), and the sex-by-PAT interaction term was significant (0.02). Results were similar after adjusting for the same factors as above in model 2 (age, race, history of diabetes mellitus, hypertension, previous myocardial infarction, subjective ratings of distress, β-blocker use, and resting RPP). Again, Gensini score, depression, antidepressant use, angina, and functional capacity were considered as potential confounders in model 2, but were not included because the results did not change. After adding RPP response and percent ischemia with conventional stress, results remained similar, although slightly attenuated (model 3). Baseline PAT amplitude was available in a subgroup of 308 participants. Women had significantly lower baseline amplitude values compared with men (390.7 versus 680.1; $P<0.0001$). After adjusting for baseline amplitude in this subsample, the main findings did not change, and in fact, the results were further away from the null in women.

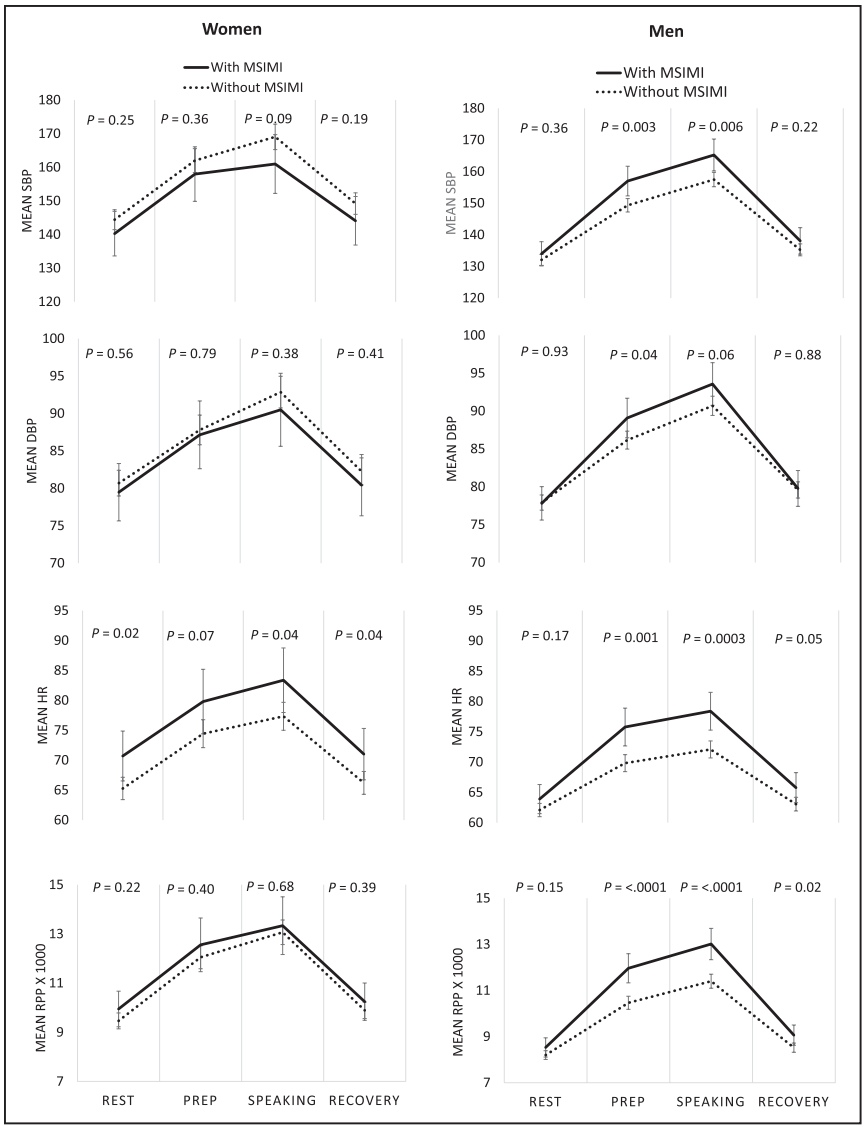

Figure 1. Comparison of hemodynamic changes in women and men with and without mental stress-induced myocardial ischemia (MSIMI) during mental stress testing. Hemodynamic changes measured as systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and rate-pressure product (RPP). All measurements are adjusted for body surface area. Error bars represent 95% confidence intervals.

Bland–Altman plots showed good reproducibility of mental stress on cardiovascular responses and stress-induced myocardial ischemia with Tc99m sestamibi (Figure I in the online-only Data Supplement). For systolic blood pressure, 95.5% of data points were within the 95% limits of agreement (I-a). Results were similar for diastolic blood pressure (I-b), heart rate (I-c), and RPP (I-d). For PAT ratio (I-e), reproducibility results were similarly excellent, with only 1 data point falling outside the 95% limits of agreement. When we calculated reproducibility of MSIMI with Tc99m sestamibi of 19 patients who had repeated testing 2 weeks apart,[21] only 2 data points were outside the 95% limits of agreement (I-f). Bland–Altman plots were also used to compare agreement between the 2 readers' SPECT (single-photon emission computed tomography) sum stress scores of perfusion defects at rest (n=601), after mental stress (n=600), and after conventional stress (n=584). Of all data points, 94.5% were within the 95% limits of agreement for scores at rest (I-g), 94.3% for scores with mental stress (I-h), and 94.3% (I-i) for conventional stress. However, it should be noted that, to minimize variability in the interpretation of the imaging results, discrepancies were resolved by consensus or a third reader if needed.

Discussion

To our knowledge, this is the first study to empirically investigate sex-specific vascular mechanisms of MSIMI. Our findings suggest that MSIMI is primarily driven by microvascular vasoconstriction in women, whereas in men, it is driven by supply–demand mismatch because of increased hemodynamic workload.

Despite growing research on the mechanisms and outcome of MSIMI, this phenomenon remains understudied among women. Until recently, the majority of studies on MSIMI have included few or no women.[6] Recently, we and others reported that women, especially younger women, develop MSIMI more often than men.[8–10] We now show that women and men differ in vascular response patterns that predict MSIMI. These new findings complement previously observed sex differences in MSIMI and may help identify distinct stress-related risk pathways in women and men that could aid future interventions.

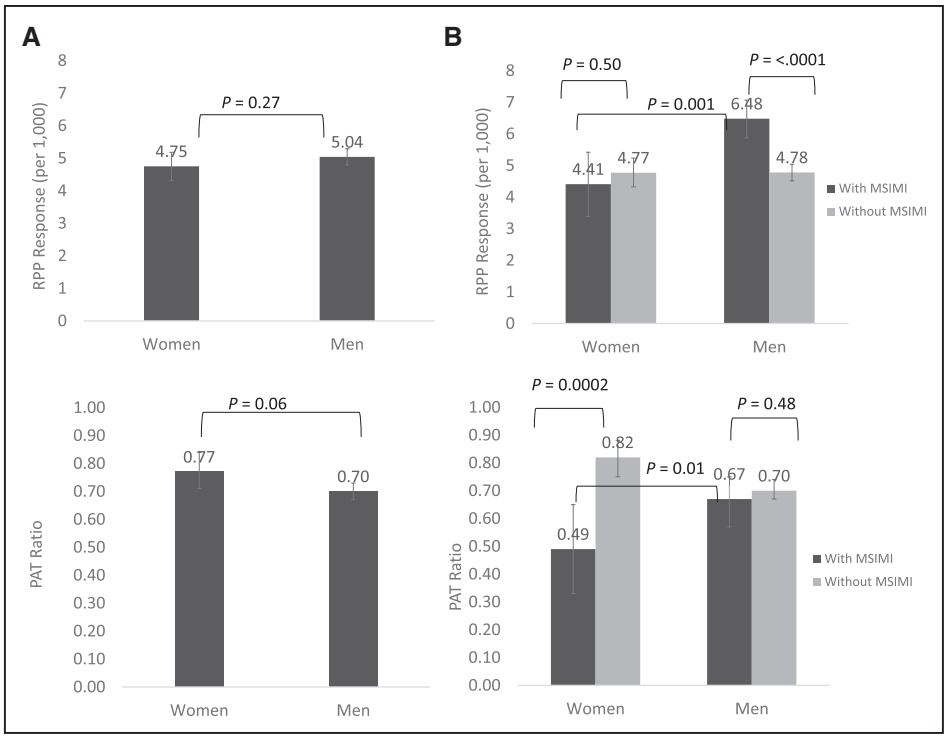

Figure 2. Hemodynamic and vascular responses. Comparison of pulsatile arterial tonometry (PAT) ratio and rate-pressure product (RPP) response in women and men (**A**), and by mental stress-induced myocardial ischemia (MSIMI) status (**B**) during mental stress testing. RPP response is calculated as the difference between maximum value during stress and minimum value during rest. The PAT ratio is calculated as the ratio of pulse wave amplitude during the speaking task over the resting baseline, with lower values indicating greater vasoconstriction. All measurements are adjusted for body surface area (BSA). Error bars represent 95% confidence intervals.

Overall, we found that women and men had similar RPP responses to mental stress. These results are similar to other studies that did not find hemodynamic differences to mental stress between men and women.[8,22,23] However, other studies reported greater hemodynamic responses to mental stress among men.[10,24] The relationship between hemodynamic responses to mental stress and MSIMI has also been inconsistent to date, with some studies showing no association,[25–27] whereas others reported a positive association.[11,28] However, little is known about whether the association between hemodynamic reactivity with stress and MSIMI differs in men and women. Although York et al[22] did not directly address this question, they found no sex differences in hemodynamic responses overall and among patients who

Table 2. Sex-Specific Associations of Hemodynamic and Vasoconstrictive Measures With Mental Stress-Induced Myocardial Ischemia

	Outcome: Percent Increase in Left Ventricular Inducible Ischemia by Mental Stress									
	RPP Response* per 1000-U Increase					PAT Ratio† per 0.10-U Decrease				
	Women	*P* Value	Men	*P* Value	*P* Value of Sex* RPP Interaction	Women	*P* Value	Men	*P* Value	*P* Value of Sex* PAT Interaction
	β (95% CI)		β (95% CI)			β (95% CI)		β (95% CI)		
Model 1	−0.10 (−0.26–0.06)	0.21	0.28 (0.19–0.38)	<0.0001	<0.0001	0.23 (0.11–0.35)	0.0001	0.05 (−0.04–0.15)	0.27	0.02
Model 2	−0.09 (−0.25–0.07)	0.27	0.32 (0.22–0.42)	<0.0001	<0.0001	0.23 (0.11–0.35)	0.0002	0.06 (−0.04–0.16)	0.24	0.03
Model 3	−0.12 (−0.33–0.10)	0.28	0.24 (0.13–0.35)	<0.0001	0.004	0.22 (0.10–0.34)	0.0003	0.05 (−0.05–0.14)	0.35	0.03

Model 1: RPP response and PAT ratio are in separate models. Adjusted for sex, BSA, and sex interaction term. Model 2: RPP response and PAT ratio are in separate models. Adjusted for model 1 covariates+age, race, diabetes mellitus, hypertension, β-blocker, previous myocardial infarction, subjective units of distress scale, and resting RPP. Model 3: RPP response and PAT ratio are included in the same model. Adjusted for model 2 covariates and %LV conventional stress-induced myocardial ischemia. BSA indicates body surface area; CI, confidence interval; LV, left ventricle; PAT, pulsatile arterial tonometry; and RPP, rate-pressure product.

*RPP response is calculated as the difference between maximum value during stress and minimum value during rest.

†The PAT ratio is calculated as the ratio of pulse wave amplitude during the speaking task over the resting baseline, with lower values indicating greater vasoconstriction.

developed MSIMI. In contrast, we found that men who developed MSIMI had a larger increase in RPP than women who developed MSIMI and that the stress-induced RPP change was associated with MSIMI only in men. These sex differences persisted after adjusting for differences in BSA, cardiovascular risk indicators, and even occurrence of ischemia with conventional stress testing. These inconsistent findings may be because of low statistical power because previous studies included only a small number of women.

When comparing PAT ratio in women and men overall, we found that men exhibited a marginally lower PAT ratio, which is consistent with results from a previous study by Hassan et al.[23] To our knowledge, however, ours is the first study to empirically compare stress-induced vasoconstrictive responses between men and women in relation to MSIMI provocation. Our findings support a vulnerability of women toward vasoconstriction-induced MSIMI, suggesting that stress-induced vasomotor responses are more likely to induce MSIMI in women than in men. In the absence of MSIMI, however, women have similar or slightly less vasoconstriction with stress than men. Our observation of these sex-specific effects in relation to MSIMI could explain some of the inconsistencies in the previous literature.

Although exact mechanisms for the observed sex differences are unknown, women's proclivity to vasoconstriction-induced MSIMI may operate through an imbalance between vasodilating and vasoconstricting mediators regulating the endothelium, resulting in microvascular dysfunction. Increased sympathetic tone during mental stress induces vasoconstriction of peripheral arteries, especially in the microvascular bed, through α_1 adrenergic receptor activation; an endothelin-1-dependent pathway may also be implicated.[13,29,30] This differs from physical exertion, where a vasodilator response predominates through a β_2 adrenoceptor mechanism. Research has suggested that MSIMI is partly mediated by microvascular dysfunction in response to mental stress and may be a potential mechanism by which young women have a higher risk of MSIMI.[4,7,14,16,31,32] Microvascular dysfunction is commonly seen in women with chest pain, even in the absence of significant epicardial coronary obstruction.[33,34] Women may also exhibit more microvascular dysregulation and endothelial dysfunction with stress. Research has suggested that repeated and cumulative exposure to stress can lead to microvascular dysfunction leading to myocardial diastolic dysfunction.[35,36] These vascular effects could be accentuated in young women given their higher baseline levels of inflammation.[37] It has also been hypothesized that women have greater vasomotor reactivity with stress than men,[9,31,38,39] in part, because they have smaller coronary arteries.[9,39,40] However, we observed sex differences in vasoconstriction-induced MSIMI even after adjusting for BSA.

Our empirical research findings validate previous reports postulating an important role of stress-induced vasoconstrictive responses in relation to MSIMI among women.[4,14,16,31] Thus, coronary microvascular dysfunction and vasoconstriction may be important in understanding why women have a greater propensity for MSIMI compared with men. Understanding women's increased risk of MSIMI through vasoconstriction identifies a high-risk population that may benefit from stress mitigation techniques or other tailored interventions.[7] With regard to pharmacological interventions, combined α- and β-blockers might be beneficial in these patients if microvascular dysfunction is the substrate for their ischemia.[41]

There are several strengths and limitations of our study worth noting. First, the MIPS study provides one of the largest and most comprehensive studies of MSIMI to date. The large and diverse sample size, including a sizable number of women, along with state-of-the art myocardial perfusion imaging, are important strengths. The experimental manipulation of the exposure (mental stress) allows a controlled assessment of the effects of hemodynamic and peripheral vascular changes on the risk of MSIMI. A limitation worth noting is the smaller number of women relatively to men, which may have limited the study power for some analyses. However, our results point to a clear demarcation of associations between women and men, with statistically significant interactions which argue against a type II error. Moreover, the relatively modest incidence of MSIMI precluded examination of subgroups, especially young women, who have shown a high proclivity toward MSIMI in previous research.[8–10] Although there was no difference in MSIMI between women and men overall, younger women did have more ischemia with mental stress than men of similar age, as reported in a separate article based on the same cohort of participants.[9] Also, even though our sample was well characterized and we have carefully examined potential confounding factors, we cannot rule out unmeasured confounders, such as perceptions of difficulty, anxiety, engagement, or lower effort. Also, the baseline amplitude was not available in all participants for analysis involving the PAT ratio. Another limitation is the lack of long-term follow-up data, which is currently underway. Finally, we relied on peripheral indicators of increased microvascular tone and were not able to assess vasomotion responses to stress in the coronary bed.

In conclusion, we found that women and men have distinct cardiovascular reactivity responses associated with MSIMI. Our results support a more prominent microvascular role in the development of MSIMI among women than men and, conversely, a more prominent hemodynamic role in the development of MSIMI among men. These data are consistent with the notion of an important role of microvascular constriction in ischemic heart disease among women and its relation with emotional stress. Furthermore, these results provide motivation for further research to understand sex differences in the effects of mental stress on cardiovascular responses, ischemia, and long-term outcomes.

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Disclosures

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Highlights

- This is the first study that has empirically investigated sex-specific patterns of cardiovascular reactivity, including hemodynamic response and peripheral vasoconstriction, in relation to mental stress-induced myocardial ischemia.
- Greater peripheral vasoconstriction was associated with mental stress ischemia only in women, whereas greater hemodynamic response was associated with mental stress ischemia only in men.
- These associations remained significant even after adjustment for age, race, medical conditions and body surface area, and conventional stress-induced myocardial ischemia.
- Women and men have distinct cardiovascular reactivity mechanisms for mental stress-induced myocardial ischemia.