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Sex differences in vascular and endothelial responses to acute mental stress

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Abstract

Objective—Our objective was to assess the differences in systemic vascular and endothelial function in response to acute mental stress between men and women. The endothelium plays a pivotal role in vascular homeostasis and the development of atherosclerotic heart disease. The mechanism and presentation of cardiovascular events show a sex-based difference, although the sex difference in the vascular and endothelial response to mental stress is not known.

Methods—Male ($n = 34$) and female ($n = 53$) subjects participated in a series of three different mental stress tasks during which vascular response was measured non-invasively using peripheral arterial tonometry. Endothelial function was assessed using reactive hyperemia peripheral arterial tonometry. Double product (systolic blood pressure $\times$ heart rate) was calculated.

Results—Males had a greater double product response ($27.2 \pm 3.6\%$ increase in double product vs. $19.2 \pm 1.7\%$; $P = 0.01$), and a greater vascular reactivity to mental stress. Females demonstrated a reduced response to reactive hyperemia (-0.47 vs. 13.74% ; $P = 0.01$). Furthermore, a subgroup of females who showed the least vaso-reactivity to mental stress showed the greatest decline in endothelial function ($-10.5 \pm 4\%$ vs. $17.4 \pm 6.3\%$; $P < 0.001$).

Interpretation—This study demonstrates sex-based differences in the vascular and endothelial responses to mental stress. The mental stress-induced reduction in endothelial function and increased double product seen in the females might manifest clinically as contributing to the pathophysiology of mental stress-mediated cardiovascular events in female patients and provide further information regarding the potential mechanism for sex differences in cardiac events.

Keywords

sex; mental stress; endothelial function; peripheral arterial tonometry

Introduction

Women have had a trend of an increasing morbidity and mortality rate from acute coronary syndromes since 1984 [6,7]. Although previous studies have demonstrated the role of traditional risk factors, such as the Framingham risk profile, in the mechanism of the

presentation of coronary artery disease [12], these studies are done mostly in men. The increased incidence of non-obstructive heart disease in women and unique sex-differences in risk factors may highlight the need to explore non-traditional risk factors in women [1,22].

The discrepancy between the incidence of cardiovascular-related deaths in women and men may be related to the sex-based differences in the mechanism of cardiovascular disease and cardiac events in women [1,22]. It has been speculated that particularly in women the mechanism of cardiovascular events may be secondary to more functional abnormalities such as endothelial dysfunction and microvascular disease [14,16,25,26].

This may shed light on the differing trends in cardiovascular related deaths in men and women, when considering that endothelial dysfunction has been shown to be an independent risk factor for increased cardiovascular disease in patients without coronary artery disease, especially in women [1]. Furthermore, the role of the psychosocial stressors of daily life that trigger emotions [11,18,19] as important independent risk factors in the development and progression of functional abnormalities in the endothelium and cardiovascular disease, especially in women, has continued to emerge and requires further investigation [8,15,20].

Considering these factors, along with the lack of adequate characterization of sex-based differences in response to vascular reactivity and endothelial function to mental stress in normal populations, the present study was designed to test the hypothesis that there is an underlying sex-based difference in the vascular response to acute mental stress; compared to men, women have 1) reduced endothelial function in response to mental stress, as demonstrated by a greater reduction in reactive hyperemia peripheral arterial tonometry ratios following mental stress testing and 2) reduced vascular reactivity to mental stress, as demonstrated by lower peripheral arterial tonometry mental stress ratios during mental stress testing.

Methods

This study protocol was reviewed and approved by the Institutional Review Board, Mayo Clinic and Foundation. Written informed consent was obtained from each participant. Male and female subjects were recruited for this study and asked to fast for 4 hours prior to the study, and abstain from coffee or tobacco the day of the examination.

Experimental protocol

All studies were performed in a quiet, temperature controlled and uniformly lit room. Subjects were seated comfortably in a padded chair with armrests. A fitted blood pressure cuff was placed on one arm, and the finger cuffs of the peripheral arterial tonometry (EndoPAT 2000) device, as described in a subsequent section, attached to the middle finger of each hand.

Endothelial function was evaluated before and immediately after an acute mental stress protocol in each subject. Subjects relaxed for 10 minutes before baseline blood pressure and heart rate were obtained via a digital automated blood pressure cuff (Omron Healthcare, Inc., Vernon Hills, Illinois, USA). Peripheral arterial tonometry signal recording was then started, and following a baseline peripheral arterial tonometry measurement, the first reactive hyperemia protocol was performed. Subjects were allowed to relax for a further 5 minutes before the start of the sequence of mental stress tasks.

Blood pressure and heart rate measurements were taken 30 seconds before, 2 minutes into, and at the end of each 6-minute mental stress task, which are described in a later section. Subjects had 5-minute baseline rest periods between each mental stress task, during which they were instructed to relax. At the end of the final (third) mental stress task, the reactive hyperemia

protocol was repeated. Double product was calculated as systolic blood pressure multiplied by heart rate.

Peripheral arterial tonometry

Peripheral arterial tonometry signals were obtained using the EndoPAT 2000 device (Itamar Medical Inc. Ltd, Caesarea, Israel), which has been validated and used previously to assess peripheral arterial tone in other populations [3,9]. The finger probes were comprised of a system of inflatable latex air cuffs connected by pneumatic tubes to an inflating device controlled through a computer algorithm. A constant counter pressure (pre-determined by baseline diastolic blood pressure) was applied through the air cushions. This prevented venous pooling thus avoiding veno-arteriolar reflex vasoconstriction. There was no occlusion of arterial blood flow.

Pulsatile volume changes of the distal digit induced pressure alterations in the finger cuff, which were sensed by pressure transducers and transmitted to and recorded by the EndoPAT 2000 device. A decrease in the arterial blood volume in the distal finger tip caused a decrease in pulsatile arterial column changes, reflected as a decrease in the measured peripheral arterial tonometry signal, and vice versa.

The PAT response to mental stress in patients with cardiovascular disease has been reported previously [16]. There is a characteristic peripheral arterial tonometry signal response to mental stress, with diminution of the signal amplitude during stress (Figure 1). A ratio of the stress peripheral arterial tonometry amplitude to baseline peripheral arterial tonometry amplitude (peripheral arterial tonometry mental stress ratio) of 0.8 or less is considered a positive response to mental stress and considered a marker for future stress-related cardiovascular events [9].

Reactive hyperemia protocol

Endothelial function was measured via a reactive hyperemia-PAT index. The method has been previously described [3,4]. A reactive hyperemia protocol consists of a 5-minute baseline measurement, after which a blood pressure cuff on the test arm was inflated to 220 mmHg for 5 minutes. After 5 minutes, the cuff was deflated, and the peripheral arterial tonometry tracing recorded for a further 6 minutes. The ratio of the peripheral arterial tonometry signal after cuff release compared to baseline was calculated through a computer algorithm automatically normalizing for baseline signal, and indexed to the contra-lateral arm. The calculated ratio reflects the reactive hyperemia-PAT index.

Mental stress protocol

The mental stress testing protocol was administered under the supervision of a licensed clinical psychologist. Following the first reactive hyperemia trial and a subsequent rest period, the three different mental stress tasks of 6-minute duration and in random order were performed. All tasks had intra-test levels of varying difficulty and were externally paced to accentuate the induced mental stress [17].

The tasks consisted of a number-letter recall challenge of increasing length and complexity (spiral omnibus), number subtraction of increasing difficulty (1 digit from 2 digits, up to 3 digits from 3 digits), and a computerized version of the Stroop word-color conflict. The Stroop word-color conflict test consisted of three colored words (red, blue, and green) displayed in random order on a computer screen. Each word could appear in either its own color (visually concordant), or in one of the other two colors (visually discordant). The subject's task was to enunciate the color of the word, not the actual word itself. A rectangular box surrounded the stimulus color-word, and this task was also externally paced, with the subject having to keep pace with the advancing box.

Statistical analysis

Results are expressed as mathematical mean $\pm$ standard deviation. Repeated measures analysis of variance (ANOVA) was used to assess differences between treatment groups and levels. Differences between groups were analyzed using unpaired t-test. Statistical significance was accepted at $P < 0.05$.

Results

The baseline population demographics are shown in Table 1. A total of 87 volunteers with an average age of 38 ± 1.5 years and a total of 34 males and 53 females were studied. Male subjects had a higher body mass index, as compared to female subjects ($P = 0.04$). There were no significant differences in age, or the prevalence of cardiovascular disease risk factors, between the two groups ($P > 0.05$). As compared to male subjects, females had significantly lower triglyceride ($P = 0.02$) and low-density lipoprotein ($P = 0.05$) levels, and higher high-density lipoprotein levels ($P = 0.0002$) respectively.

The mean arterial pressure before and after mental stress testing was 88.7 ± 1.1 and 98.0 ± 1.3 mmHg for the group respectively ($P < 0.0001$); the average increase in heart rate after mental stress testing was 6.71 ± 0.7 beats/minute ($P < 0.0001$), representing an average $22.3 \pm 1.8\%$ increase in double product after mental stress for the whole group. Compared to females, following mental stress males showed greater increases in mean arterial pressure (11.4 ± 1.0 vs. 7.94 ± 0.9 mmHg, $P < 0.001$) and heart rate (7.60 ± 1.3 vs. 6.14 ± 0.8 beats/minutes, $P < 0.005$), resulting in an increased double product response to mental stress of 27.2 ± 3.6 vs. $19.2 \pm 1.7\%$, $P = 0.01$; Figure 2).

The absolute systolic, diastolic, and mean arterial blood pressures and heart rate values for men and women before mental stress testing (pre-testing) and during each of the three mental stress tests is shown in Table 2. As shown in the table, each systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate value for both men and women were significantly higher during each of the three mental stress tests as compared to baseline (pre-testing) values ($P < 0.05$ for each pressure and heart rate value pre-testing vs. mental stress test). Furthermore, as shown in the table, systolic blood pressure, and, therefore, mean arterial blood pressure values, were higher in men compared to women at baseline (pre-testing) and during each of the three mental stress tests ($P < 0.05$ for each systolic blood and mean arterial pressure value in men vs. women).

The peripheral vascular response to mental stress as measured by the ratio of stress to baseline peripheral arterial tonometry signal amplitude tended to be greater in males than females (0.79 ± 0.07 vs. 0.9 ± 0.04 respectively, $P = 0.07$).

Endothelial function, as manifested by reactive hyperemia-PAT index, showed that there was a significant difference in peripheral endothelial function, or reactivity, after acute mental stress testing between male and female subjects. In response to mental stress, male subjects had an increase in reactive hyperemia response, as evidenced by the increase in reactive hyperemia-PAT index compared to female subjects, who showed a decline in peripheral endothelial function (13.7% vs. -0.47% , $P = 0.01$; Figure 2).

In addition to the above data analysis, we also subdivided the group of subjects according to overall vascular reactivity in response to mental stress (Table 3). We classified subjects into either the "reactive" or "non-reactive" groups based on their peripheral arterial tonometry mental stress response to mental stress. Those who had a peripheral arterial tonometry mental stress ratio of <0.8 on 2 or more mental stress tests were categorized as 'reactive' ($n = 42$). Those who had a peripheral arterial tonometry mental stress ratio of >0.8 on 2 or more mental

stress tests were categorized as ‘non-reactive’ to mental stress ($n = 45$) [9]. Mean age was similar between the groups. There was a greater proportion of females in the non-reactive group compared to the reactive group (76 vs. 45%).

The average peripheral arterial tonometry mental stress ratio in the reactive vs. the non-reactive group was 0.61 vs. 1.09 respectively ($P < 0.0001$). There tended to be a greater hemodynamic response (reflected as % change in double product) to mental stress in the reactive compared to the non-reactive group (24.5 vs. 20.3%, $P = 0.1$). The non-reactive group had a significant decline in peripheral endothelial function after mental stress compared with the reactive group ($-5.1 \pm 4.1\%$ vs. $16.0 \pm 4.3\%$ respectively, $P < 0.001$).

Females who were non-reactive to mental stress (as defined by change in peripheral arterial tonometry amplitude) had a smaller change in double product, but a marked decline in endothelial function in comparison to females who were reactive to mental stress ($-10.5 \pm 4.0\%$ vs. $17.4 \pm 6.3\%$, $P < 0.001$; Figure 3). This decline in peripheral endothelial function was also greater than the entire female cohort as a whole ($-10.5 \pm 4.0\%$ vs. $-0.47 \pm 3.9\%$ respectively, $P < 0.05$). In contrast, females who were reactive to mental stress showed a peripheral endothelial function response to cumulative mental stress similar to that of both reactive and non-reactive males.

Discussion

The current study demonstrates that in a group of subjects without any significant history of ischemic heart disease, there appears to be two temporally distinct responses to acute mental stress. The first observed response is immediate, and characterized by an increase in heart rate, systolic and diastolic blood pressure, resulting in an increased double product. This first phase is most likely associated with an increase in peripheral vascular tone, as evidenced by changes in the amplitude of the peripheral arterial tonometry signal. Both these responses were more prominent in male subjects compared to female subjects.

The second observed temporally distinct response to mental stress appears to be on endothelial function. Furthermore, there appears to be a cumulative effect of mental stress testing on endothelial function. This is supported by our finding of a sex-based difference in reactive hyperemia following cumulative mental stress between male and female subjects. Male subjects demonstrated a significantly higher increase in reactive hyperemia, as compared to female subjects. Female subjects showed no change, with a trend towards worsening of endothelial function, or reduced endothelial reactivity, compared to baseline. The current study provides a potential mechanism to reported differential myocardial ischemia responses to mental stress between men and women.

There was also a dichotomy in the peripheral vascular response to mental stress, with some individuals being more vaso-reactive and showing greater decrements in post-stress peripheral arterial tonometry amplitude than others. These subjects were, therefore, categorized as ‘reactive’ females and ‘reactive’ males. The rest of the subjects, who demonstrated a reduced reactivity to mental stress, were categorized as non-reactive females or ‘non-reactive’ males. Reactive females and reactive males behaved similarly, with an improvement in endothelial function after mental stress. The ‘non-reactive’ females showed a significant decline in endothelial function after mental stress, especially when compared to the reactive subgroup of females. This decline was also greater than the entire female cohort as a whole, and may manifest as increases in cardiovascular disease risk factors or onset as this group of relatively young subjects ages.

Possible mechanisms

The initial vascular responses to mental stress may be due to increased sympathetic tone [5, 21]. Our observations of an immediate increase in heart rate, systolic and diastolic blood pressure in male and female subjects following mental stress, suggesting increased peripheral sympathetic vascular tone, support this idea. Furthermore, if the normal response to mental stress is one of sympathetic arousal, and increased peripheral vascular tone, as evidenced by a decrease in peripheral arterial tonometry mental stress ratio and an increase in systolic blood pressure, then indeed in those patients with pre-existing cardiovascular and coronary artery disease, exaggerated vascular reactivity to mental stress might be a marker for future events. This sex-based difference in peripheral vascular reactivity and increased systolic blood pressure, mean arterial pressure, and double product in response to mental stress in normal healthy male subjects might also be a factor in the earlier presentation of hypertension, stroke, and coronary artery disease in men [24].

It could be argued that the decline in endothelial function in women is not an abnormality as such, but a normal physiological response to a smaller vasoconstriction. However, the reduction in vascular reactivity to mental stress and reactive hyperemia may suggest that women are unable to increase myocardial blood flow to compensate for reduced myocardial oxygen tension during myocardial ischemia and, therefore, are more prone to cardiovascular disease [1,22]. Furthermore, women have a higher incidence of non-obstructive coronary related deaths than men, possibly due to speculation that the mechanism of cardiovascular events in women may be secondary to more functional abnormalities such as endothelial dysfunction and microvascular disease [14,16,25,26].

The novel finding in the present study of a sex difference in vascular and endothelial response to mental stress, along with the findings from previous studies [2,16] of a close correlation between mental stress and incidence of coronary artery disease, strongly support a need for further studies in the area of decreased vasoreactivity to mental stress and increased cardiovascular and coronary artery disease incidence, morbidity and mortality especially in women.

Our study is unique in that both male and female subjects were recruited and also peripheral vascular reactivity was measured, as well as endothelial function responses to mental stress. This allowed direct comparison of sex differences in vascular and endothelial responses to mental stress. In the present study, peripheral endothelial function response to mental stress was assessed using reactive hyperemia-PAT response rather than flow-mediated brachial artery dilatation as used in other studies [8,21]. The advantages of this system are that since a finger probe is placed on each hand, the non-study (contra-lateral) arm of the subject effectively acts as an intra-subject control, and differences in baseline vascular tone during the pre-stress and post-stress studies can be corrected for. However, we cannot exclude that differential activity of sympathetic tone and baseline vasoconstriction may affect the difference between men and women. Nonetheless, the assessment of endothelial function by this method takes into account environmental factors affecting the baseline vascular tone. Furthermore, in previous studies from our lab, we demonstrated high degrees of sensitivity and specificity of using peripheral arterial tonometry (EndoPAT 2000) technology for measuring endothelial function with high correlation with measures of peripheral arterial tone to the current Gold Standard of coronary artery endothelial function assessment (the coronary blood flow response to intra-coronary acetylcholine-infusion) [4].

The current study reports for the first time a significant sex-based difference in endothelial function response to mental stress. Females who showed little or no change in the acute peripheral vascular response to acute mental stress also demonstrated a marked decline in peripheral endothelial function after cumulative mental stress. This occurred regardless of the

order in which the three mental stress tests were performed. The functional significance of this observation may be speculated. The acute impairment in endothelial function may potentially lead to myocardial ischemia [10].

There are several limitations to this current study. First, our sample size is relatively small. Comparatively however, it did exceed the size of most other study populations characterizing cardiovascular and endothelial responses to mental stress [8,23]. We also did not have an equal number of male and female subjects. The difference in number of subjects between groups seemed to have minimal effects on the results, as there was not significant variability in our measurements. Another of the limitations of the current study is we did not measure serum levels of neurohumoral factors such as catecholamines or endothelin that may be involved in the mechanism of the sex-differences in vascular responses.

Finally, we did not correlate our studies with specific time points of menstrual cycles or oral contraceptive use in female subjects. There is minimal evidence that suggests that there may be some difference in endothelial-dependent vasodilation as measured by flow-mediated vasodilation, but there is also evidence that although hormonal fluctuations may alter sympathetic outflow, it doesn't effect the transduction of sympathetic activity into vascular resistance [13]. Additionally, the present studies involved acute comparison of each subject to herself on the same day. Although menstrual cycle phase may influence endothelial function, the gender differences we observed in the present study occurred independently of any potential menstrual cycle effect.

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Fig. 1. Peripheral arterial tonometry tracing showing a reactive response to mental stress. There is a >20% decrement in signal height during mental stress compared to baseline

Fig. 2.

Sex Differences in double product and reactive hyperemia response to mental stress. Data is expressed as mean percent change $\pm$ standard deviation from baseline to after acute mental stress testing. * $P = 0.01$ males vs. females for both double product and reactive hyperemia

Fig. 3.

Double product and reactive hyperemia response to mental stress in reactive and non-reactive males and females. Data is expressed as mean percent change $\pm$ standard deviation from baseline to after acute mental stress testing. * $P < 0.05$ reactive females vs. non-reactive females for both double product and reactive hyperemia

Table 1

Demographics of study population

	Male (<i>n</i> = 34)	Female (<i>n</i> = 53)	<i>P</i> value
Age (years)	37.9 ± 2.4	37.5 ± 2.0	NS
Body mass index (BMI)	30.8 ± 1.3	27.8 ± 0.8	0.04
Total cholesterol (mg/dl) ^a	184.1 ± 6.6	170.4 ± 6.1	NS
Triglycerides (mg/dl) ^a	130 ± 12.3	92.5 ± 10.4	0.02
HDL (mg/dl) ^a	50.9 ± 2.8	66.5 ± 2.6	0.0002
LDL (mg/dl) ^a	101.5 ± 6.5	84.7 ± 5.0	0.05

Values expressed as mean ± SEM

^a
n = 51

Table 2
Blood pressure and heart rate values during pre-testing and mental stress testing in males and females

Mental stress test	Males (n = 34)				Females (n = 53)			
	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR
Pre-testing	128 ± 13 [†]	75 ± 9 [†]	93 ± 10 [†]	69 ± 10 [†]	119 ± 16 ^{*,†}	71 ± 10 [†]	87 ± 11 ^{*,†}	65 ± 10 [†]
Stroop color word	139 ± 18	83 ± 10	102 ± 12	75 ± 10	128 ± 19 [*]	80 ± 11	96 ± 13 [*]	73 ± 13
Mental arithmetic	137 ± 18	84 ± 11	102 ± 12	75 ± 11	126 ± 22 [*]	79 ± 10	95 ± 13 [*]	73 ± 12
Spiral omnibus	136 ± 20	82 ± 12	100 ± 14	73 ± 11	126 ± 20 [*]	76 ± 17	93 ± 16 [*]	70 ± 12

Values expressed as mean ± SEM

SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure, HR heart rate

* P < 0.05 for both SBP and MAP in males vs. females

[†] P < 0.05 for pre-testing SBP, DBP, MAP, and HR values vs. mental stress test values in both males and females

Table 3

Hemodynamic and reactive hyperemia response to mental stress in reactive and non-reactive groups (male and female subjects combined)

	Age (years)	% change in DP	PAT-R	% change in RH
Reactive (<i>n</i> = 42)	36.3 ± 2.2	24.5 ± 3.0	0.61 ± 0.02	16.0 ± 4.3
Non-reactive (<i>n</i> = 45)	38.9 ± 2.2	20.3 ± 2.0	1.09 ± 0.04	-5.13 ± 4.1
<i>P</i> -value	0.2	0.1	<0.001	<0.001

Values expressed as mean ± SEM

DP double product, *PAT-R* peripheral tonometry ratio, *RH* reactive hyperemia