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Gender-Related Differences in the Sympathetic Vasoconstrictor Drive of Normal Subjects.

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ABSTRACT

The risk of cardiovascular disease has been linked to sympathetic activation and its incidence is known to be lower in women than in men. However, the effect of gender on the sympathetic vasoconstrictor drive has not yet been established. We planned to find out whether there is a gender difference in muscle sympathetic nerve activity (MSNA) and blood flow, and to determine the mechanisms involved.

We examined 68 normal subjects, 34 women and 34 men, matched for age, BMI and waist circumference. MSNA was measured as the mean frequency of single units (s-MSNA) and as multi-unit bursts (m-MSNA) from the peroneal nerve simultaneously with its supplied calf muscular blood flow (CBF).

Women had lower ($P=0.0007$) s-MSNA (24 ± 2.0 impulses/100 cardiac beats) than men (34 ± 2.3 impulses/100 cardiac beats), and a greater baroreceptor reflex sensitivity controlling efferent sympathetic nerve activity than men. The sympathetic activity was inversely and directly correlated respectively to CBF ($P=0.03$) and calf vascular resistance (CVR) ($P=0.01$) in men only. The responses of an increase in CVR to cold pressor and isometric handgrip tests were significantly smaller in women ($P=0.002$) than in men despite similar increases in efferent sympathetic nerve activity.

Women had a lower central sympathetic neural output to the periphery, the mechanism of which involved differences in central and reflex control, as well as a lower vasoconstrictor response to this neural output. It is suggested that this may partly explain the observed lower incidence of cardiovascular events in women compared to men.

Introduction

The level of arterial blood pressure and the incidence of cardiovascular disease, including hypertension, in middle-aged populations have been reported to be lower in women than in men [1-6]. However, despite the widely accepted relationship of sympathetic activation to the pathogenesis and cardiovascular complications of hypertension [7,8], the influence of gender on the sympathetic vasoconstrictor drive has not yet been established.

For instance firstly, there have been no published reports designed primarily to investigate gender-related differences in the levels of resting muscle sympathetic nerve activity (MSNA). Also, the information that is available from studies in which results have been obtained in men and women have been separately presented showing women to have either lower [9-14] or similar [12,14-17] levels of resting MSNA relative to young and older men respectively.

Secondly, there has been no information regarding gender-related differences in the operation of peripheral sympathetic vasoconstrictor drive as represented by the relationship between MSNA and simultaneously measured calf muscle blood flow (CBF) and resistance (CVR). This is important because there are reports showing that such a relationship is influenced by local vaso-active, hormonal, and structural factors [18-20]. Indeed, it is well known that levels of MSNA do not necessarily correlate to those of arterial pressure between individuals [20-22].

We therefore planned to find out whether the mean frequency of efferent muscle sympathetic activity and calf muscular blood flow in normal women are different from those in matched normal men, and to determine the mechanisms involved. For this purpose, we simultaneously used microneurography directly to quantify efferent MSNA from the peroneal nerve and standard venous occlusion plethysmography to measure CBF during the steady state, cold pressor and isometric handgrip tests.

Methods

Subjects

We prospectively examined 68 normal Caucasian subjects. They comprised 34 women and 34 men. All had similar sedentary occupational status and dietary habits including a sodium intake of ≈ 400 mmol/d, and none was engaged in exercise training. They were screened by history and physical examination, and none was obese or had evidence of hypertension, arrhythmia, neuropathy or chronic conditions that may influence the autonomic nervous system. Twelve of the women were post-menopausal, while 6 men and 7 women gave a history of smoking. Arterial blood pressure was defined on the basis of the average of at least 3 sphygmomanometer readings, and all subjects had normal levels of systolic and diastolic arterial pressure [23]. The subjects of the two groups were matched during recruitment according to age, body mass index, and waist circumference. The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the St. James's University Hospital Ethics Committee, with all subjects providing informed written consent.

General Protocol

Microneurographic and haemodynamic measurements were obtained in an identical manner for all subjects during each session, as has previously been reported in detail [22,24]. All investigations were performed under similar conditions between the hours of 09:00 and 12:00, and subjects were asked to have had a light breakfast and to empty their bladder before commencing the study. They were instructed to avoid nicotine and caffeine products for 12 hours, as well as alcohol and strenuous exercise for 24 hours prior to the investigation. During each session, the subjects were studied in the semi-supine position when data attained a steady state for at least 30 minutes. Measurements were made in a darkened laboratory in which the temperature was constant between 22 and 24°C. Resting arterial blood pressure was measured from the arm, using a mercury sphygmomanometer. Changes in heart rate and arterial pressure were monitored and recorded, using a standard electrocardiogram and a Finometer device (FMS, Arnhem, The Netherlands, TPD Biomedical Instruments).

Microneurography

Post-ganglionic muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve, simultaneously with the other data as previously described [22,24]. The neural signal was amplified (x50,000); then, it was either filtered (bandwidth of 700-2000 Hz) and integrated (time constant 0.1 sec) for the purpose of generating bursts representing multi-unit discharge, or left intact to examine raw action potentials. The output of action potentials and bursts from this assembly was passed to a PC-based data-acquisition system (LabView, National Instruments Corp., Austin, TX, United States), which digitised the acquired data at 12,000 samples/second (16 bits).

Muscle sympathetic nerve activity (MSNA) was differentiated from skin sympathetic activity and afferent activity, as previously described [22,32]. Single units (s-MSNA) in the raw action potential neurogram were obtained by adjusting the electrode position, whilst using fast monitor sweep, and on-line storage oscilloscope to confirm the presence of consistent action potential morphology [22,32]. Only vasoconstrictor units were accepted and examined, the criteria of acceptance being appropriate responses to spontaneous changes in arterial pressure during verification by a preliminary Valsalva manoeuvre and isometric handgrip exercise. During the Valsalva manoeuvre, sympathetic nerve activity increased during the latter part of phase-II and/or phase-III and decreased during phase-IV (respectively corresponding to the decrease and increase of arterial pressure). During the isometric handgrip exercise, performed using a dynamometer (MIE Medical Research Ltd., Leeds, UK), a delayed increase of sympathetic nerve activity was observed. In addition, simultaneous measurement of calf vascular resistance confirmed the vasoconstrictor function of the observed neural activity.

Analysis was performed independently off-line, using dedicated software based on the LabView system (National Instruments Corp., Austin, TX, USA). This allowed electronic superimposition of units from the raw action potentials to establish their same morphology (s-MSNA). Then, an electronic discriminator window was used objectively to count those s-MSNA spikes with consistent morphology and a threshold discriminator was used to count the R-waves of the electrocardiogram. The mean frequency of s-MSNA was quantified over one minute and over 100 cardiac beats, to avoid any interference by the length of the cardiac cycle [26]. The multi-units bursts of

MSNA (m-MSNA) were identified by inspection when the signal-to-noise ratio was greater than 3, and were counted and quantified in a similar manner to s-MSNA. The variability of repeated measurements of two minute segments of recordings of s-MSNA units and MSNA bursts spanning a period of 30 minutes or those of two impalements performed within 60 minutes did not exceed 10%, in terms of twice the 95% confidence intervals around individual differences relative to the mean of the repeated measurements [22].

Calf blood flow

Calf blood flow (CBF) was obtained simultaneously with microneurography, using an automated mercury-in-silastic (Whitney) strain gauge venous occlusion plethysmograph (D.E. Hokanson Inc., Bellevue, WA, USA). The strain gauge was placed around the widest circumference of the left calf region, and chosen to be 2-3 cm smaller than the calf circumference, such that it was applied under slight tension to the calf. Venous occlusion was effected by inflating a contoured thigh cuff (Model CC-22, D.E. Hokanson Inc., Bellevue, WA, USA), placed around the left thigh, to about 60 mmHg or 20 mmHg below the pre-determined diastolic arterial blood pressure, whichever was the lesser. The DC output from the plethysmograph was passed to a chart recorder (APC Medical Ltd., Welwyn Garden City, Herts., UK) utilising heat sensitive paper, so that a graphic record of change in limb volume could be produced. During measurement of CBF, the left foot region was excluded by inflating a paediatric cuff placed around the ankle, to levels greater than the pre-determined systolic arterial blood pressure.

CBF was obtained typically at 3 recordings per minute during periods of steady state conditions. The average of the recordings was expressed in units of $\text{ml} \cdot 100\text{ml}^{-1} \cdot \text{min}^{-1}$. The intra-observer reproducibility of CBF measurement in this laboratory, obtained as twice 95% confidence interval of differences between repeated within-session plethysmography, amounted to 2.4% of the value of the measurement. Arterial blood pressure was simultaneously and continuously measured, and its average value was divided by the average CBF, to obtain calf vascular resistance (CVR), which was expressed in arbitrary units.

Other measurements

Responses of haemodynamic variables and sympathetic nerve activity to formal isometric handgrip exercise (IHG) and cold pressor (CPT) tests were measured. The former was performed at 30% of a pre-determined maximal voluntary contraction for two minutes and the latter by dipping the subject's hand into cold water with a temperature of less than 4 °C for at least one minute or until discomfort was felt. Baseline and recovery data were taken for 1 minute prior to, and after each of the two tests. CPT was performed by all women and 32 men, while IHG was performed by 33 women and 31 men. The responses of sympathetic nerve activity and its vascular effect were obtained in 33 women and 31 men during CPT, and 30 women and 32 men during IHG; in the remaining subjects, it was not possible to obtain the activity because of interference by changes in leg muscle tension and inability to tolerate cold exposure. Responses to isometric handgrip exercise were derived from the differences between data obtained during the second minute of the exercise, when sympathetic activity is known to increase [27], and the average of those obtained during baseline and recovery periods. Responses to cold pressor test were derived as the differences between data obtained during the last 30 seconds of exposure to cold, when the occurrence of discomfort is known to be accompanied by an increase of sympathetic activity [28], and the average of those obtained during baseline and recovery periods.

Baroreceptor reflex sensitivity controlling the heart period mainly through vagal effects (BRS-hp/sbp) and that controlling s-MSNA (BRS-sna/dbp) were obtained by a standardised Valsalva manoeuvre and measured independently off-line, using the LabView software. Subjects performed the manoeuvre to between 40 and 50 mmHg for 15 seconds. BRS-hp/sbp was obtained in all subjects, while BRS-sna/dbp was obtained in 28 women and 28 men. To obtain the BRS-hp/sbp, the time interval during which the rise of arterial blood pressure occurred in stage IV of the Valsalva manoeuvre was identified and each systolic arterial blood pressure value and its corresponding heart period (phase 0) and the succeeding one (phase 1) were analysed. BRS-hp/sbp was calculated from the slope [29,30] of the best significant linear relationship between the systolic arterial blood pressure and its heart period (phase 0) or the succeeding one (phase 1). BRS-sna/dbp was calculated in a similar manner by relating the diastolic arterial pressure values to the number of s-MSNA corrected for the length of the heart

period over nine beats following each index arterial pressure. A close relationship of sympathetic nerve activity to short-term changes in diastolic arterial blood pressure has previously been observed [21,31,32].

Statistical analysis

Unpaired Student *t* tests were used to assess differences of data and absolute responses between the two groups. Percentage responses relative to control values were compared using the Mann-Whitney test. The least square technique was used for assessing the linear relationship between variables. Values of $P < 0.05$ were considered statistically significant. Data were presented as mean \pm SEM.

Results

The two groups were matched according to the design of the investigation in respect of age, body mass index (BMI), waist circumference and heart rate (Table 1). Men were taller and had slightly higher arterial blood pressure values than women.

Compared to the group of men, women had significantly lower indices of sympathetic nerve activity (Fig. 1), lower BRS-hp/sbp and higher BRS-sna/dbp (Fig. 2). No significant group differences were found between women and men regarding CVR (41 ± 2.0 and 44 ± 2.4 units; $P > 0.30$) or CBF (2.3 ± 0.08 and 2.4 ± 0.13 ml.100ml.⁻¹ min.⁻¹; $P > 0.36$). However, in men the indices of sympathetic nerve activity were positively correlated to CVR (at least $r > 0.38$, $P < 0.002$) and negatively correlated to CBF (at least $r > -0.32$, $P < 0.035$), with no such significant correlations in women (respectively at least $r < 0.29$, $P > 0.058$ and $r < -0.194$, $P > 0.136$). Figure 3 depicts the relationship between these variables in men and women.

The responses to CPT of the two groups are depicted in Fig. 4. Both groups of women and men had similar responses of heart rate, mean arterial blood pressure and sympathetic nerve activity to CPT. The respective percentage changes for women and men for heart rate ($10\pm 1.5\%$ and $8\pm 1.4\%$), mean arterial pressure ($22\pm 2.2\%$ and $20\pm 1.7\%$), m-MSNA ($86\pm 17.2\%$ and $53\pm 8.9\%$) and s-MSNA ($120\pm 20.4\%$ and $103\pm 21.9\%$) were not significantly different (at least $P > 0.20$). However, the response of

increase of CVR was significantly smaller in women than in men (Fig. 4); similarly its percentage increase was less ($P<0.004$) in women ($46\pm 5.9\%$) than in men ($88\pm 17.1\%$).

In respect of the responses to IHG of both groups, women had significantly smaller increases in heart rate and arterial blood pressure (Fig. 5). The percentage increases of heart rate ($9\pm 1.3\%$) and mean arterial pressure ($14\pm 1.4\%$) in women were smaller respectively ($P<0.001$ and $P<0.001$) than those in men ($21\pm 2.7\%$ and $27\pm 2.6\%$). Both women and men groups had similar responses of sympathetic activity to IHG (Fig. 5), though in terms of percentage changes the women showed greater increase ($P<0.03$) of m-MSNA ($113\pm 21.4\%$) than men ($57\pm 8.6\%$). The percentage increase of s-MSNA was also greater in women ($195\pm 35.4\%$) than in men ($57\pm 8.6\%$), though this was not statistically significant ($P>0.07$). However, the increase in CVR was smaller in women than in men (Fig. 5) and its percentage increase in women ($28\pm 3.0\%$) was smaller ($P<0.001$) than in men ($69\pm 9.6\%$).

Discussion

Our study has demonstrated in normal women and men that there were gender-related differences in the level of MSNA, its vascular effect and its baroreceptor reflex control. The original and salient findings have included firstly a lower central sympathetic output to the periphery in women than in men, brought about by a greater baroreceptor reflex inhibitory effect by arterial blood pressure. Secondly, the vasoconstrictor effect of the peroneal sympathetic nerve activity was attenuated in women as compared to men, and this occurred both at resting conditions and during sympathetic activation.

Regarding group characteristics of men and women, some of our findings have already been previously reported. Thus, women have been found to be shorter [5,9,16,17,33-35], to have a lower body weight [9,16,17,33,34,36-38], a slightly lower arterial blood pressure [2,5,34,37-40] and higher heart rate [5,33,34,38,41] than men that were at least matched for age. These similarities could be considered to rule out the arguments that our subjects were not representative of other reported studies involving women and men.

Our previous findings and those of others have helped to design our study, in respect of avoiding confounding factors that can interfere with sympathetic nerve activity. This was achieved by matching individuals of the two groups. Subjects of both groups were Caucasians and were examined using the same protocol and under similar laboratory conditions whilst avoiding the influence of age, gender, dietary intake, general or regional obesity, large meal or visceral distension; these factors are known to affect sympathetic activity or its control [9,12,14,21,25,26]. Pre- and post-menopausal women were examined, as it has been shown that the onset of menopause does not affect the level of MSNA [14]. The finding of slightly lower levels of arterial blood pressure in women was associated with a lower rather than higher sympathetic nerve activity than in men, a finding that is not consistent with an inhibitory effect through baroreceptor reflex control of sympathetic nerve activity. Also, the differences in sympathetic nerve activity between women and men were greater than the variability attending repeated measurements of this activity [22]. These considerations make it likely that the observed gender differences in sympathetic nerve activity were not solely caused by differences in the levels of arterial blood pressure or other factors known to affect the sympathetic output.

Our finding of a lower level of efferent sympathetic nerve activity in women than in men is similar to data found in the majority of other reports. For instance, six of nine studies have reported significantly lower sympathetic nerve activity in young and middle aged women than men [9-14]. In the remaining three reports, either women were found to have lower sympathetic activity than men when examined at the same arterial blood pressure [16] or the lower group average of sympathetic activity in women was not significantly different from that in men [15,17]. Of the three studies that examined older men and women, one found lower sympathetic activity in women than in men [9], while the other two [20,22] did not. Similarly, resting calf vascular resistance has been reported to be similar in women and men [15,42]. Our study, which was primarily designed to test the possibility of gender-related differences, has established that non-obese and normal middle-aged women had lower resting efferent sympathetic nerve activity than men.

In both women and men, IHG and CPT caused significant increases in efferent sympathetic nerve activity and arterial blood pressure. This was not unexpected because

the rise in arterial blood pressure that brings about a baroreceptor reflex inhibitory effect on efferent sympathetic activity and the rise of this activity in response to IHG and CPT are subject to complex interactions that include central effects [27,31,32,43,44]. Previously reported data have not been consistent regarding a gender effect on the responses of arterial pressure and sympathetic activity to IHG [9,11,36]. In the present study, the responses of arterial blood pressure to IHG were smaller in women, while the absolute increases of sympathetic nerve activity were similar to those in men leading to a greater percentage increase in women. In respect of CPT, the increases of arterial blood pressure and sympathetic activity in women were similar to those in men. Similar findings have previously been reported [9,11,13,42].

The mechanisms of the lower resting efferent sympathetic nerve activity in women were shown in this study to involve a greater baroreceptor reflex inhibitory control of this activity in women than in men. The BRS-sna/dbp in women was steeper than in men, and was accompanied by an impaired BRS-hp/sbp in women relative to men. The latter has previously been found using the Valsalva manoeuvre as in the present study [39], using neck suction [34] as well as when changing arterial blood pressure levels by pharmacological agents [40,41]. As such our method of examining baroreceptor reflex control has yielded similar results to those obtained using other techniques. In respect of the control of efferent sympathetic nerve activity, previously reported studies in animals and humans have indicated that females have a greater central and baroreceptor reflex inhibitory control of this activity than males [45,46]. Our study has now established that women have a greater baroreceptor reflex inhibitory control of the sympathetic activity, and also found a smaller control of heart rate that is mainly mediated by withdrawal of vagal effects. These considerations are consistent with the findings in this study of a lower resting sympathetic nerve activity and higher heart rate in women than in men.

Another new finding of our study was the demonstration that the vasoconstrictor effect of the efferent sympathetic activity in women was attenuated relative to that in men. This was apparent in the relationship between the sympathetic activity and either CVR or CBF that was found only in men; greater sympathetic activity was associated with greater CVR and lower CBF in men and not in women. In addition, women had a smaller increase of CVR than men during augmentation of efferent sympathetic activity by CPT and IHG. Previously reported studies, mainly in animals, have found an

attenuated vascular response to sympathetic stimulation in females [46]. The present investigation has now established such gender-related difference in humans.

In the present study we quantified the central output of sympathetic nerve activity to the periphery, and as such this could differ from that destined to supply visceral organs [8]. However, in normal subjects a correlation has been reported between MSNA and the sympathetic drive to the heart and the kidney as assessed by norepinephrine spillover rate [47,48]. Furthermore, it has been reported that men have a predominance of sympathetic effects on the heart interval using spectral analysis of the heart rate [16,37,39,49,50], and higher circulating catecholamine levels than women [11,35,38]. These reported findings are consistent with our results of an existing difference in the sympathetic drive between women and men.

Our findings raise clinical implications regarding gender differences in respect of conditions related to sympathetic activation. For instance, the level of arterial blood pressure and the incidence of cardiovascular disease, including hypertension, have been reported to be lower in middle-aged women than in men of similar age [2,3]. Indeed, a lower prevalence of cardiovascular disease has been documented in women than in men [1,4,6]. These reports could be explained on the basis of our findings of a lower level of sympathetic output and its attenuated vasoconstrictor effect.

In conclusion our study has demonstrated that women have a lower central sympathetic nerve activity to the periphery, the mechanism of which involved a greater baroreceptor reflex inhibitory effect on this activity in women than in men. The study also demonstrated an attenuated vasoconstrictor effect of peroneal efferent sympathetic nerve activity in women than in men. These findings could have implications regarding the lower cardiovascular events observed in women than in men.

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Table 1. Data of the two groups of 34 women and 34 men.

Variable	Women	Men	Significance <i>P</i>
Age (years)	43±2.2	45±2.6	Ns
Body weight (kg)	69±1.7	83±1.6	<0.0001
Height (cm)	165±1.0	179±1.3	<0.0001
BMI (kg/m ²)	25±0.6	26±0.5	Ns
Waist circumference (cm)	84.9±1.8	87.2±2.0	Ns
Heart rate (beats/minute)	64±1.2	61±1.6	Ns
Mean ABP (mmHg)	93±1.3	96±1.0	0.04
Systolic ABP (mmHg)	123±1.8	128±1.6	0.04
Diastolic ABP (mmHg)	78±1.0	80±1.0	Ns
s-MSNA (impulses/100b)	39±3.6	58±3.8	0.0003
s-MSNA (impulses/min)	24±2.0	34±2.3	0.0007
m-MSNA bursts (bursts/100b)	33±3.1	50±3.8	0.0007
m-MSNA bursts (bursts/min)	21±1.8	29±2.3	0.0026
CBF (ml.100ml. ⁻¹ min. ⁻¹)	2.3±0.08	2.4±0.13	Ns
CVR (units)	41±2.0	44±2.4	Ns
BRS-hp/sbp (ms/mmHg)	5.3±0.40	7.2±0.55	0.0035

Data as mean ± SEM. BMI (body mass index). ABP (arterial blood pressure). m-MSNA (multi-unit muscle sympathetic nerve activity) and s-MSNA (single unit muscle sympathetic nerve activity) expressed per 100 cardiac beats (100b) and per minute (min). *P* values refer to two tailed unpaired *t* tests, ns as *p* ≥ 0.05

Figure 1.

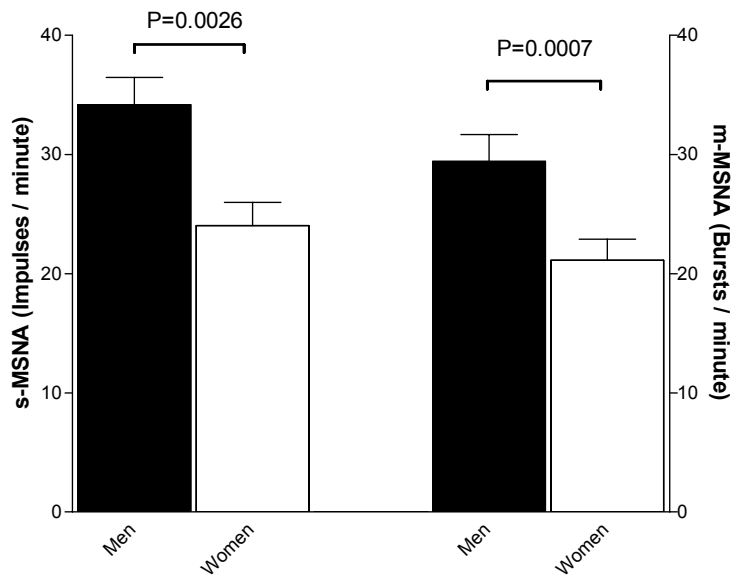
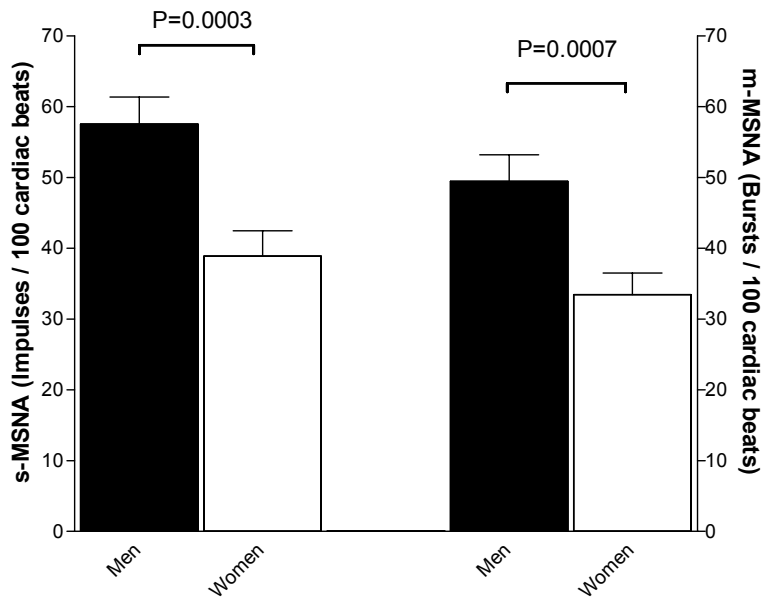


Figure 2.

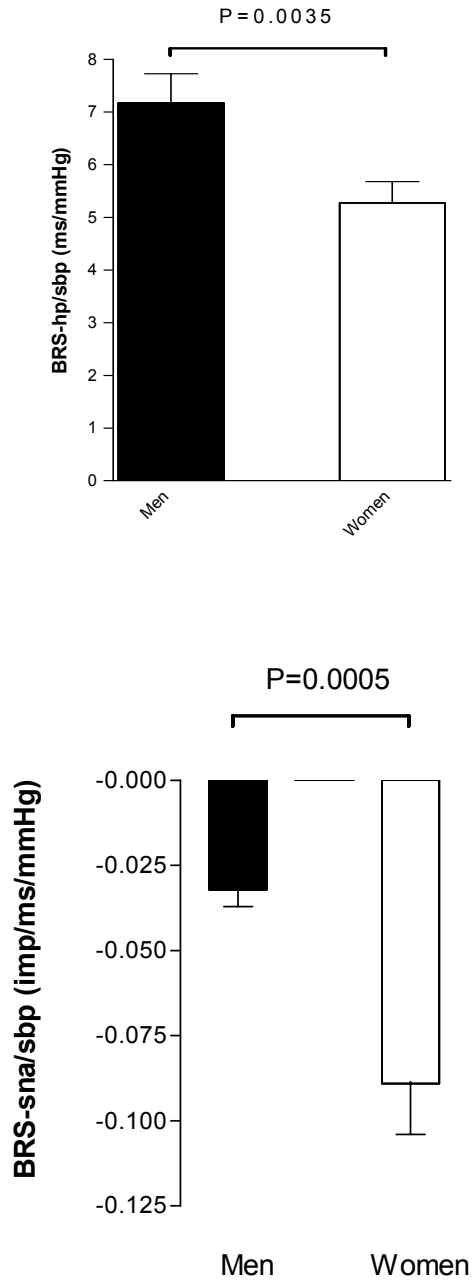


Figure 3.

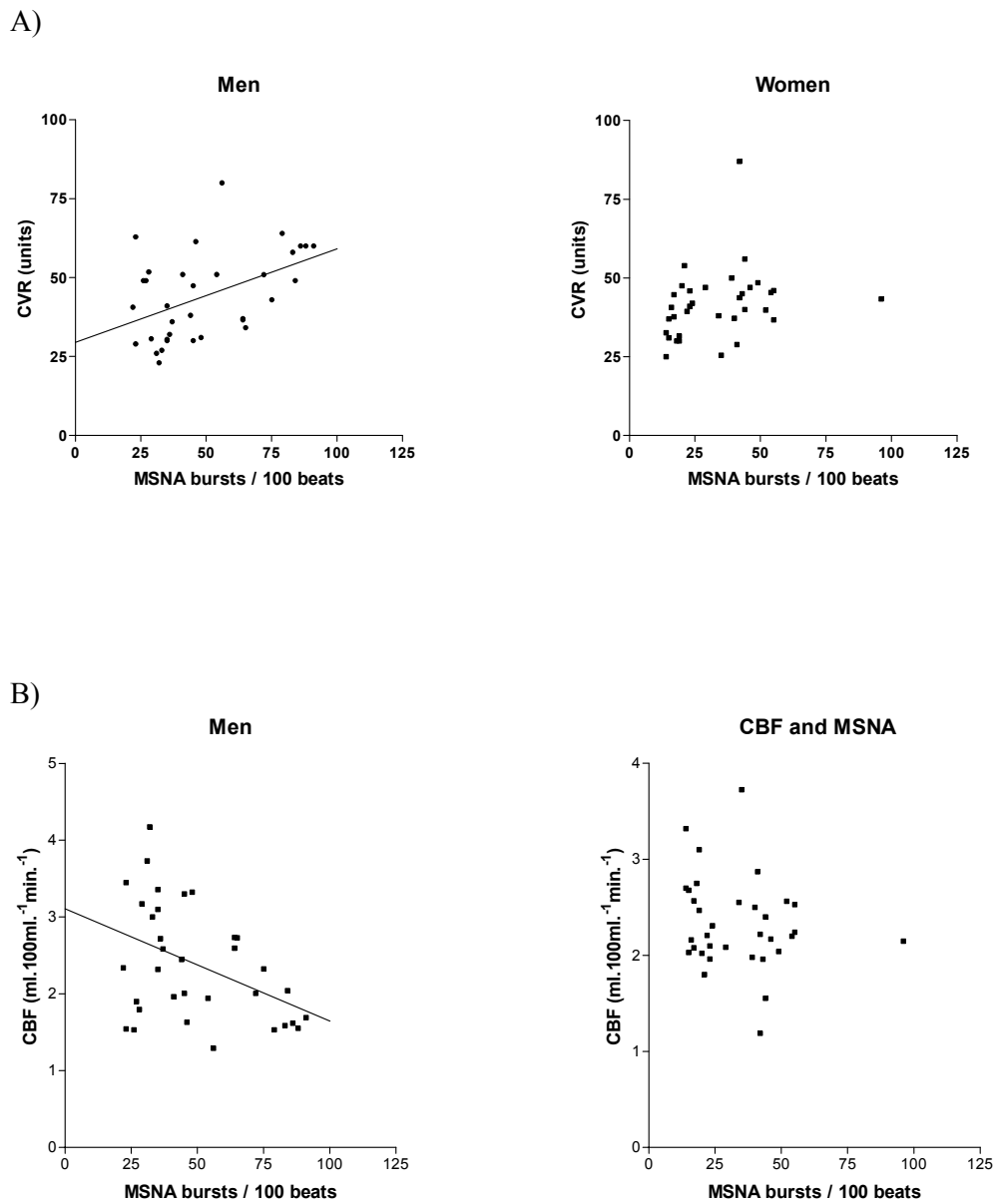


Figure 4.

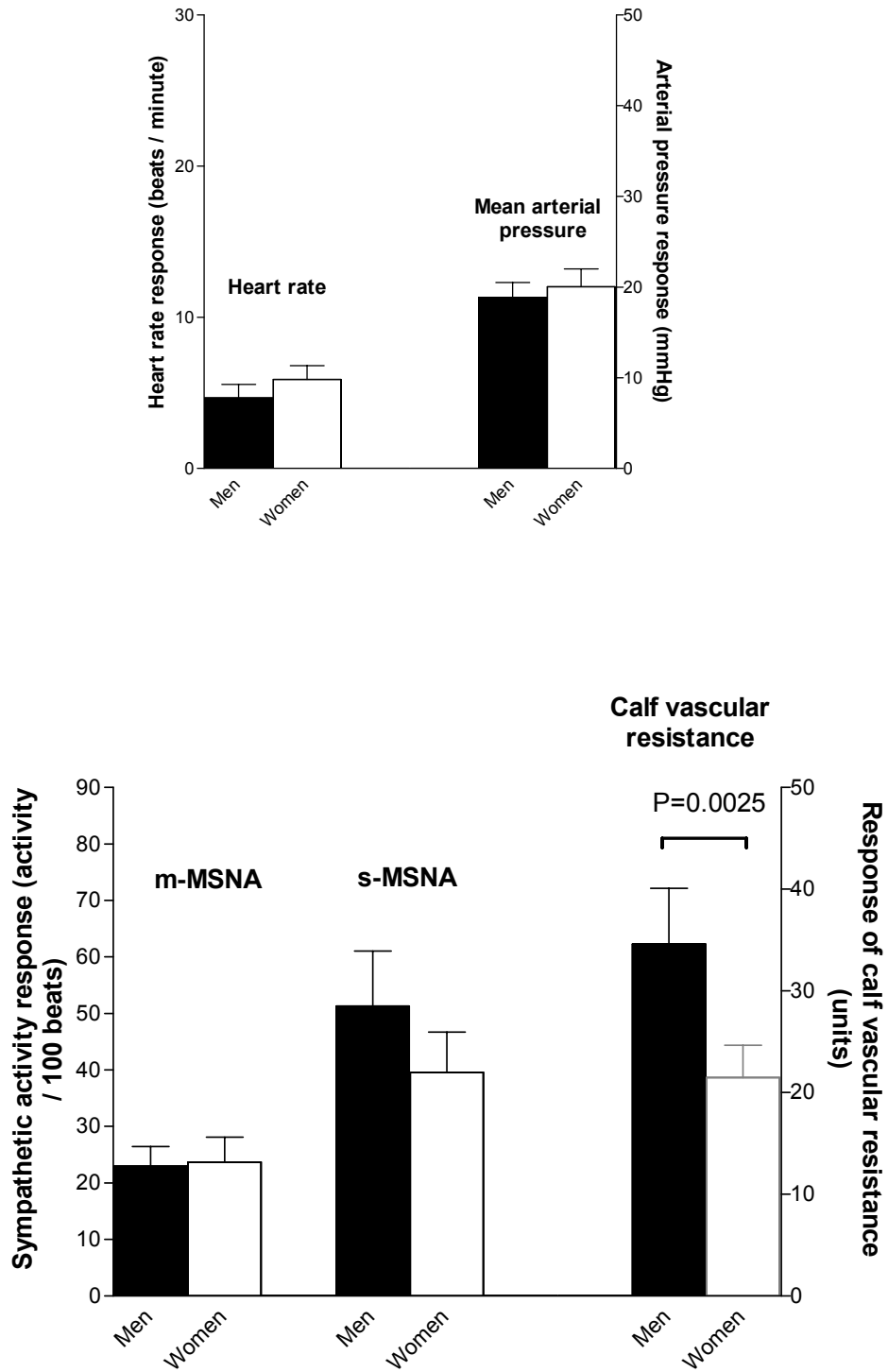


Figure 5.

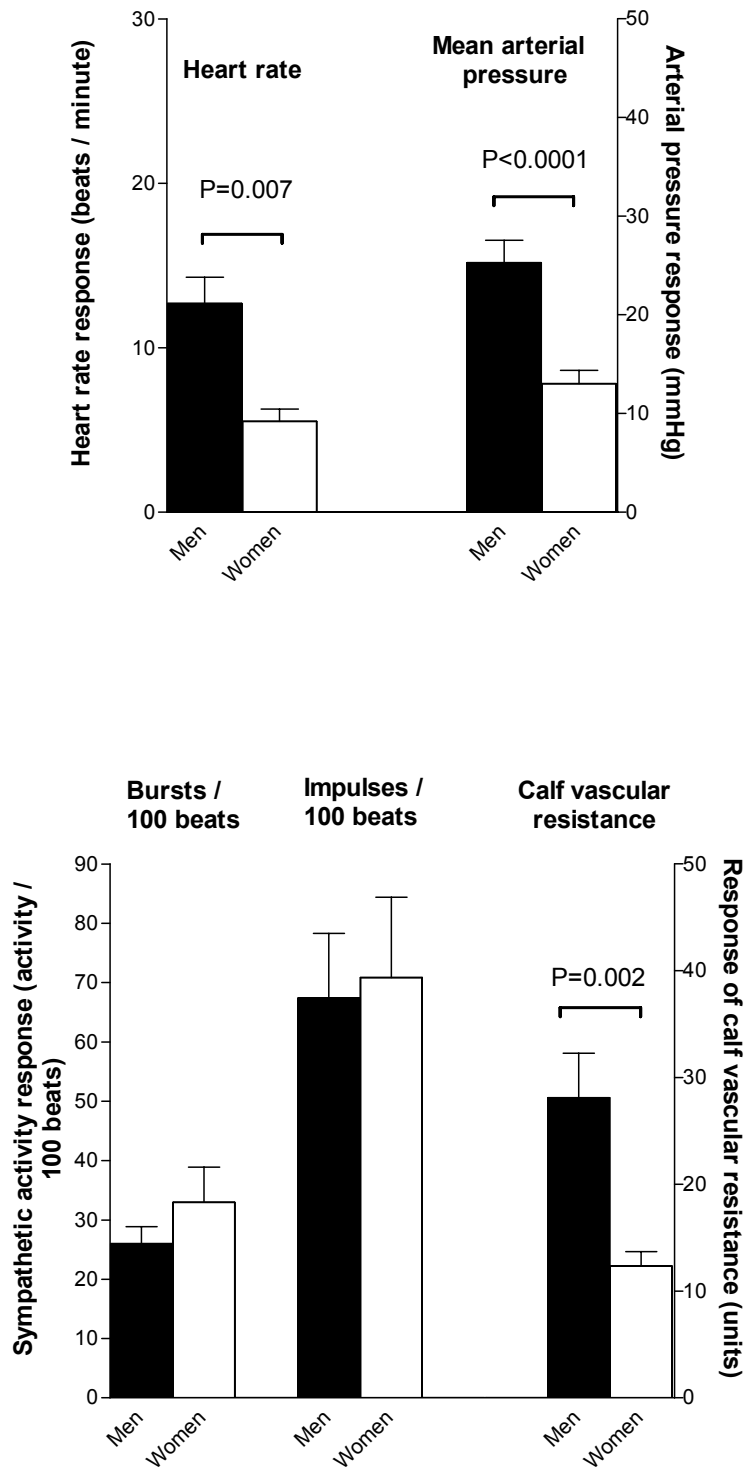


Figure Legends

Figure 1. Levels of m-MSNA (multi-unit muscle sympathetic nerve activity) and s-MSNA (single unit muscle sympathetic nerve activity) expressed per 100 cardiac beats (top) and per minute (bottom) for men and women. *P* values refer to unpaired *t* tests when significant. The height of the column denotes mean of groups and the bars SEM. Women have lower sympathetic activity than men.

Figure 2. Baroreceptor reflex sensitivity for men and women. BRS-hp/sbp refers to the control of the heart period (top) and BRS-sna/dbp to the control of efferent sympathetic nerve activity (bottom). *P* values refer to unpaired *t* tests, the column denotes mean of groups and the bars SEM. Women have lower BRS-hp/sbp and greater BRS-sna/dbp than men.

Figure 3. The relationship of MSNA (bursts/100beats) to A) CVR and B) CBF in men (left) and women (right). MSNA was positively correlated to CVR and negatively correlated to CBF on men with no such significant correlations in women.

Figure 4. Absolute responses of heart rate and mean arterial blood pressure (top), and of m-MSNA, s-MSNA and calf vascular resistance (bottom) to cold pressor test for men and women. *P* values refer to unpaired *t* tests. The height of the column denotes mean of groups and the bars SEM. Women have an attenuated increase in CVR in response to cold pressor test relative to men.

Figure 5. Absolute responses of heart rate and mean arterial blood pressure (top), and of m-MSNA, s-MSNA and calf vascular resistance (bottom) to isometric handgrip test for men and women. *P* values refer to unpaired *t* tests. The height of the column denotes mean of groups and the bars SEM. Women have an attenuated increase in calf vascular resistance in response to isometric handgrip test relative to men.