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RELATIONSHIP BETWEEN SYMPATHETIC NERVE ACTIVITY AND AORTIC WAVE REFLECTION CHARACTERISTICS IN POSTMENOPAUSAL WOMEN

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Abstract

OBJECTIVE—Aortic wave reflection characteristics, such as augmentation index, are positively related to muscle sympathetic nerve activity in young men. In young women, there is an inverse relationship. We investigated whether this inverse relationship persisted in postmenopausal women.

METHODS—Muscle sympathetic nerve activity (peroneal microneurography) and arterial pressure (brachial catheter) were measured in 16 postmenopausal women (age; mean $\pm$ SEM, 60 $\pm$ 2 yrs.). Aortic blood pressure and wave form characteristics were synthesized from radial arterial pressure waves (applanation tonometry). Specifically, augmentation index, wave reflection amplitude and estimated wasted left ventricular energy were calculated. These data were compared to our previously published work from an identical protocol in 23 young women (25 $\pm$ 1 yrs.).

RESULTS—Tonic sympathetic activity was higher in postmenopausal vs. young women (64 $\pm$ 3 vs. 24 $\pm$ 4 bursts/100 heart beats). All indices of aortic wave reflection were higher in the postmenopausal vs. young women ($P < 0.05$). Baseline sympathetic activity was inversely related to augmentation index ($r = -0.63$, $P < 0.05$), augmented pressure ($r = -0.62$, $P < 0.05$) and wasted left ventricular energy ($r = -0.61$, $P < 0.05$) in young women. Conversely, baseline sympathetic activity was positively related to augmentation index ($r = 0.63$; $P = 0.09$), augmented pressure ($r = 0.69$, $P < 0.05$) and wasted left ventricular energy ($r = 0.79$, $P < 0.05$) in postmenopausal women.

CONCLUSIONS—High levels of sympathetic activity are associated with higher indices of aortic wave reflection in postmenopausal women. Consequently, postmenopausal women with high sympathetic activity may be more at risk of developing cardiovascular disease or adverse cardiovascular related events.

Keywords

aortic pressure; sympathetic nerve activity; menopause; women; pressure wave reflection

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Conflicts of interest: None

Introduction

In women, the risk of developing cardiovascular disease (e.g. hypertension) and experiencing cardiovascular related events (e.g. stroke) increases following menopause.¹⁻³ This is associated with a gradual increase in arterial pressure as women age, which becomes more markedly elevated around the onset of menopause.¹ The increase in arterial pressure in aging women, is associated with a concomitant increase in sympathetic nerve activity^{4, 5} and stiffening of the large elastic arteries.^{6, 7} Increased arterial stiffness causes an elevation in pulse wave velocity which can have a profound effect on central aortic pressures. In this context, 'stiffer' vessels promote early return of pressure waves which are reflected back to the heart from peripheral sites. Consequently, the pressure waves arrive early during systole instead of diastole. Early return of pressure waves causes an elevation in ascending aortic systolic and pulse pressure, which in turn causes an increase in afterload. In general, increased amplitude of the reflected pressure waves, to the heart, is associated with increased risk of experiencing adverse cardiovascular events.⁸⁻¹⁰ Along these lines, it is well documented that postmenopausal women have an elevation in arterial stiffness^{6, 7} and consequently increased indexes of aortic wave reflection.^{11, 12}

We recently reported that among young men, muscle sympathetic nerve activity (MSNA) is positively related to indexes of aortic wave reflection.¹³ Therefore, men with high MSNA had higher indexes of aortic wave reflection. However and interestingly, we found that among young women this relationship became negative. That is, young women with high MSNA had lower indexes of aortic wave reflection. This suggests that in young men, high levels of MSNA negatively affect aortic hemodynamics to a greater extent than in young women and identifies further mechanisms by which the female sex hormones modify cardiovascular risk factors and protect the cardiovascular system from the detrimental effects of high sympathetic nerve activity. Whether this apparent protective mechanism is abolished in postmenopausal women is unknown. Therefore, we hypothesized that in postmenopausal women, sympathetic nerve activity would have a negative effect on indexes of aortic wave reflection, similar to that observed in young men but not in young women. Thus, the aim of this study was to examine whether there was a relationship between MSNA and indexes of aortic wave reflection in postmenopausal women. We compared a group of postmenopausal women to data from the young women who participated in our previous study.¹³

Methods

Participants

After the protocol was approved by the Institutional Review Board of the Mayo Clinic, 19 postmenopausal women gave written informed consent to participate in this study (Table 1 for demographics). However, we could not obtain sympathetic recordings in 3 of the postmenopausal women. Therefore, the data reported represents that from 16 postmenopausal women. In addition, data from our previous study in 23 young women¹³ were used for comparison with our present group of older women. The participants were non-smokers with no history of cardiovascular or other chronic diseases and were recreationally active. One postmenopausal woman had a history of smoking, but ceased 4 years prior to the experiment. Participants were excluded if their body mass index was ≥ 28 kg/m² or if they were taking any anti-hypertensive medications. Young women taking oral contraceptives were included in this study. Postmenopause was defined as at least one year since last menstruation.¹⁴ Postmenopausal women on hormone therapy were excluded from this study. All women of child bearing age were asked to complete a pregnancy test at least 48 hours before the study day. Young women were tested in the low hormone phase of their cycle (during the placebo phase for oral contraceptives and luteal phase for normally

menstruating women). Participants fasted overnight and were asked not to consume caffeine or alcohol for 24 hours before the experiment. All study protocols were performed according to the Declaration of Helsinki.

Measurements

All studies were performed in a Center for Translational Science Activities (CTSA) based Clinical Research Unit laboratory at the Mayo Clinic, where ambient temperature was controlled between 22°C and 24°C. On arrival to the laboratory, participants rested in the supine position during instrumentation. A 20 gauge, 5 cm catheter was placed in the brachial artery of the left arm under aseptic conditions after local anesthesia (2% lidocaine). The catheter was connected to a pressure transducer, which was positioned at the level of the heart and interfaced with a personal computer to monitor arterial pressure. A 3-lead ECG was used for continuous recording of heart rate.

MSNA was recorded with a tungsten microelectrode in the peroneal nerve, posterior to the fibular head, as described by Sundlöf and Wallin¹⁵. The recorded signal was amplified 80,000-fold, band-pass filtered (700 to 2000 Hz), rectified and integrated (resistance-capacitance integrator circuit, time constant 0.1 s) by a nerve-traffic analyzer.

The assessment of arterial wave reflection characteristics was performed non-invasively using the SphygmoCor system (AtCor Medical, Sydney, Australia) described previously.¹⁶ Briefly, high-fidelity radial artery pressure waveforms were recorded by applanation tonometry of the radial pulse in the right wrist using a “pencil type” micromanometer (Millar Instruments, Houston, Texas). The radial BP and waveforms were calibrated from the systolic and diastolic brachial artery BP (catheter). A validated, generalized transfer function was used to generate the corresponding aortic pressure waveform.¹⁷ The generalized transfer function has been validated using both intra-arterially^{17–19} and non-invasively²⁰ obtained radial pressure waves in a range of participants including coronary bypass patients (aged 49–78).²¹

Pulse wave analysis of the aortic pressure waveform provided the following key variables of interest: aortic pressures, aortic augmentation index (AI_x), AI_x adjusted for a HR of 75 beats/min ($AI_x@75\text{beats/min}$) and wasted left ventricular (LV) pressure energy (E_w), which is the component of extra myocardial oxygen requirement due to early systolic wave reflection.^{13, 16, 22} Augmentation index is adjusted for heart rate because of the inverse linear relationship between the two variables.²³ E_w can be estimated as $[(\pi/4) \times (\text{augmented pressure} \times \Delta t_r) \times 1.333]$, where 1.333 is the conversion factor for mmHg/s to dynes-cm⁻².s and Δt_r is the systolic duration of the reflected wave. Augmented pressure (AP) is defined as the difference between the first (forward wave) and second systolic shoulders of the aortic systolic blood pressure and is a result of the merging of forward and reflected pressure waves. Only high-quality recordings, defined as an in-device quality index of over 80% (derived from an algorithm including average pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform), were accepted for analysis.

Protocol

After placement of the arterial catheter, participants were asked to rest supine during instrumentation of microneurography. Once a satisfactory site for measurement of MSNA was located, 15 minutes of baseline data were recorded with the subject resting quietly. Subsequently, duplicate applanation tonometry measurements were made.

Arterial line placement was unsuccessful in 2 of the young women. Therefore, data regarding stroke volume, cardiac output and TPR are calculated in 21 of the 23 young women. In these participants, an average of 3 automated brachial blood pressure readings

were used to calibrate radial pressure waveforms during the applanation tonometry measurements.

Data Analysis

Data were collected at 240Hz, stored on a computer and analyzed off-line with signal processing software (WinDaq, DATAQ Instruments, Akron, OH). Blood pressures (systolic and diastolic blood pressures; SBP, DBP) were calculated from the arterial wave form measured from the brachial artery. Mean arterial pressure (MAP) was calculated as the time integral over the pulse pressure (PP). Beat-to-beat stroke volume was calculated from the brachial arterial pulse pressure wave by model flow analysis. Model flow computes an aortic waveform based on nonlinear pressure–volume, pressure–compliance and pressure–characteristic impedance equations, incorporating age, sex, height and body mass.²⁴ Cardiac output was calculated as the average stroke volume measured over 5 minutes multiplied by the heart rate measured over the same 5 minute rest period. Stroke volume and cardiac output under normothermic resting conditions measured using Modelflow analysis compares well to that estimated by thermodilution^{25, 26} and Doppler ultrasound²⁷. Total peripheral resistance (TPR) was calculated as MAP/cardiac output. MAP, heart rate, stroke volume, cardiac output, TPR and MSNA were averaged from the last 5 minutes of the 15 minute rest period.

Sympathetic bursts in the integrated neurogram were identified by a custom-manufactured semi-automated analysis program;^{28, 29} burst identification was controlled visually by a single investigator (ECH). The program then compensated for baroreflex latency, and associated each sympathetic burst with the appropriate cardiac cycle. All pulse wave analysis variables are reported as the mean of 2 applanation tonometry measurements for each individual.

Statistical Analyses

Group data are expressed as means $\pm$ SEMs. Differences in MSNA, hemodynamic variables, and aortic wave reflection characteristics in young and older women were evaluated using a 2-tailed independent *t* test. To access the relationships between MSNA and aortic wave reflection characteristics, linear regression analysis was performed and Pearson's correlation coefficients calculated. The critical α -level was set at 0.05, and data were analyzed using SigmaStat software (version 2.03, SPSS Inc.).

Results

Average group neural-hemodynamic and aortic wave reflection variables

Subject demographics are presented in Table 1. There were no differences in height, body mass and body surface area between the young and older women.

Table 2 outlines average group differences in neural, hemodynamic and aortic wave reflection characteristics. Stroke volume and cardiac output were lower in the postmenopausal women compared to the young women ($P < 0.05$). Total peripheral resistance and brachial and aortic pressures (apart from DBP) were greater in the postmenopausal women vs. the young women ($P < 0.05$). In addition, indexes of aortic wave reflection were higher in the postmenopausal women compared to their younger counterparts ($P < 0.05$). Therefore, the estimated E_w was greater in the postmenopausal women vs. the young women ($P < 0.05$). As expected, MSNA (burst incidence and burst frequency) were also greater in the postmenopausal group compared to the young women.

Relationships between neural-hemodynamic variables and aortic wave reflection characteristics

Previously we reported that there was no relationship of MSNA to aortic pressures (Table 3) or TPR ($r = 0.14$) in the young women.¹³ Interestingly, in older women, MSNA was positively related to TPR ($r = 0.56$, $P = 0.02$) and aortic SBP and PP (Figure 1; Table 3, $P = 0.01$). In the young women, we found that MSNA was inversely related to AI_x , AP and E_w ($P < 0.05$). In complete contrast to the young women, MSNA was positively related to AI_x ($P = 0.01$; Figure 2), AI_x at 75 beats/min ($P = 0.02$), AP and E_w ($P = 0.001$) in the older women.

Discussion

The major new finding of the present study is that the level of resting MSNA is positively related to aortic systolic and pulse pressures and indexes of aortic wave reflection in postmenopausal women. Therefore, postmenopausal women with higher MSNA, have higher aortic pressures and indexes of aortic wave reflection. These relationships are in contrast to those observed in young women, where MSNA is not related to aortic pressures and inversely related to measures of aortic wave reflection.¹³

Aortic wave reflection, aortic pressures and MSNA

In postmenopausal women we (and others) have shown that indexes of aortic wave reflection (even when normalized for heart rate), aortic blood pressures (systolic and pulse pressure), peripheral blood pressures (systolic and pulse pressures) and MSNA were elevated compared to young women.^{6, 11} These factors are independent predictors for the development of cardiovascular disease, incidence of cardiovascular related events and all-cause mortality.^{10, 30} This is in part due to the fact that early return of the reflected waves leads to an increase in aortic pressure and thus an increase in afterload.

Recently, studies have indicated that MSNA may be linked to the amplitude of the reflected pressure waves and the level of aortic arterial stiffness in humans.^{13, 31} Data from our laboratory demonstrated that MSNA was related to indexes of aortic wave reflection among individuals. Furthermore, these findings indicated that the observed relationships were dependent on sex. In this context, MSNA was positively related to aortic wave reflection characteristics in young men, but inversely related in young women. Thus, young women with higher MSNA showed a lower augmentation index, whilst young men with high MSNA had a high augmentation index.

In the present study, we demonstrate that in older women, the relationship between MSNA and aortic wave reflection characteristics is reversed compared to young women, and becomes positive so it is similar to that in young men. MSNA was positively related to augmented pressure and augmentation index in the postmenopausal women (Figure 2). This relationship persisted when augmentation index was normalized for heart rate (Table 3). Augmentation index is directly affected by heart rate, that is; augmentation index is inversely related to heart rate, so that higher heart rates caused a lower augmentation index.²³ Therefore heart rate was not driving the relationship between MSNA and augmentation in postmenopausal women. These data suggest that, postmenopausal women with high MSNA had higher amplitude of the reflected pressure wave, and vice versa in postmenopausal women with low MSNA. The elevated amplitude of the reflected pressure wave which arrives at the LV during systole causes an increase in afterload. Consequently, women with high MSNA also had a high estimate of E_w ; an index of myocardial oxygen demand and left ventricular work. E_w is the portion of the tension-time index curve attributed to earlier reflection of the pulse pressure wave which increases central aortic

pressure during systole. An increase in E_w can be interpreted as an excess amount of energy expended by the LV without a proportionate increase in flow¹⁶ and is associated with left ventricular hypertrophy²². Therefore, it is possible that high levels of MSNA in postmenopausal women can indirectly increase myocardial work and the demand placed on the LV by increasing the amplitude of the reflected pressure waves from the periphery; leading to amplified aortic pressures.

Interestingly, in the present study, there was a relationship between MSNA and aortic systolic and pulse pressure in postmenopausal women (Figure 1), which did not exist in young women or men.¹³ Consequently postmenopausal women with high MSNA had high aortic systolic and pulse pressures. This suggests that as women age, MSNA may become more important in determining central aortic pressure. This may have important consequences since elevated aortic pulse pressure is more strongly related to vascular disease and cardiovascular events than brachial blood pressures.³²

Why are the relationships opposite in young and older women?

The inverse relationship between MSNA and indexes of aortic wave reflection in young women becomes positive in postmenopausal women so it becomes similar to that in young men. This suggests a role for the female sex hormones in modifying this relationship. Along these lines recent data demonstrate a possible role for the female sex hormones in modifying the transduction of MSNA into peripheral vascular tone.³³ Exactly how the sex hormones might modulate the effect of MSNA on the vasculature is unclear. Data from our laboratory and others suggest that differences in β -adrenergic sensitivity to norepinephrine play a role.^{34, 35} For example, vasoconstriction in response to norepinephrine infusion in the forearm is enhanced following β -blockade in young women, but not in young men^{34, 35} or postmenopausal women³⁴. Thus, in young women, vasoconstrictor tone caused by norepinephrine release from the sympathetic nerve endings is offset by concurrent β -adrenergic receptor stimulation. Consequently, high levels of MSNA in young women may decrease aortic waveform characteristics via decreased vascular tone or stiffness via vascular β -adrenergic receptor stimulation. This appears to become reversed as women age and become postmenopausal. Data from our laboratory suggests that as women age this β -adrenergic vasodilator effect decreases and is minimal in post-menopausal women.³⁴

It should be noted that changes in the cardiovascular system that occur as part of a normal aging process might also have an impact on the interactions observed between indexes of aortic wave reflection and MSNA. Aging is also associated with endothelial dysfunction,^{36, 37} desensitization of α -adrenergic receptors,^{34, 38, 39} increased reactive oxygen species⁴⁰ and decreased blood volume relative to fat free mass^{41, 42}. Consequently, because we did not directly test whether the female sex hormones are involved in modifying the relationships described above in older postmenopausal women, we cannot rule out the possibility that normal healthy aging also plays a crucial role.

Limitations

Age associated increases in aortic stiffness likely contributed to the elevated baseline wave reflection characteristics we observed in the postmenopausal women (Table 2).^{6, 11} Unfortunately, we did not directly measure regional arterial stiffness (i.e. PWV) in the current study (similar to our first paper;¹³). Therefore, we are unable to determine if the relationship between MSNA and wave reflection characteristics in postmenopausal women were related to aortic PWV. Along these lines, future studies are warranted to elucidate whether the change in the relationship between MSNA and aortic wave reflection that occurs in aging women is driven by aortic stiffness.

In addition, the group of postmenopausal women may be viewed as a relatively low sample size (n=16). Since we included a smaller sample size we could not complete multiple regression analysis on our data as smaller sample sizes increase the chance that we will inflate the multiple regression correlation coefficients. In this case we may find relationships where there are none. However, the sample size included in this investigation is not different to many other studies with high impact findings involving groups of healthy postmenopausal women.^{35, 43} This is related to the fact that it is difficult to recruit healthy postmenopausal women that are not taking anti-hypertensive medications and/or hormone therapy.

Finally, concerns regarding our comparison of young women to older postmenopausal women have been raised. Since we compare young women to a much older population, it is hard to draw conclusions regarding whether differences in these populations are due to alterations in circulating levels of sex hormones or age per se. However, we also compare our data to that found in young men. In our previous publication we showed that young men with high MSNA have a high augmentation index.¹³ This was the opposite in young women, where MSNA was in fact inversely related to augmentation index. Because we can compare our group of postmenopausal women to a group of young men (as well as young women), we can hypothesize that the change we see in older women, is not purely due to the aging process. Consequently, this supports the assertion that the female sex hormones do in fact offset the effect on augmentation index and thus the afterload that the left ventricle has to contend with. This adds further evidence that in older postmenopausal women, it is important to prevent increases in sympathetic nerve activity.

Perspectives

Young women appear to be protected against the possible detrimental effects of high sympathetic nerve activity on the cardiovascular system.¹³ Interestingly, this protective effect disappears in older postmenopausal women. In older women; there is an increase in MSNA which may be due to an interaction between aging and the onset of menopause in women. Moreover, there is an alteration in the way the MSNA interacts with vasculature in postmenopausal women. Here we show evidence that postmenopausal women with high sympathetic nerve activity not only have higher levels of peripheral blood pressures, but also have higher levels of aortic blood pressure and aortic wave reflection (the latter is also a relationship which is observed in young men and not in young women). Together, these variables may increase LV workload and thus myocardial oxygen demand. The positive relationship between MSNA and aortic blood pressures, combined with a general increase in MSNA may explain why older postmenopausal women have an increased risk of developing cardiovascular diseases and cardiac related events (such as myocardial infarction). Furthermore, these data raise the possibility that when women with high levels of MSNA become menopausal, they are more likely to develop LV hypertrophy and become more at risk of experiencing CV related events.^{10, 44}

Conclusions

In summary, we found that the inverse relationship between MSNA and indexes of aortic wave reflection we previously observed in young women is positive in postmenopausal women, so it is similar to that in young men. Thus, postmenopausal women with high MSNA have higher indexes of aortic wave reflection and estimated LV work. The present data are therefore consistent with our and others' previous reports showing that the female sex hormones modulate the effects of MSNA on the vasculature.^{34, 45} Finally, the mechanisms we present in the present report likely contribute to the increased risk of cardiovascular disease and specific cardiovascular events in older women. This highlights the need to prevent rises in sympathetic activity in postmenopausal women. However, the best method to achieve this aim remains ambiguous.

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Figure 1.

Linear regression analysis of the relationship between MSNA (burst incidence) and aortic systolic blood pressure (ASBP, upper panel) and aortic pulse pressure (APP, lower panel) in postmenopausal ($n = 16$). We compared this to data collected in 23 young women in our laboratory that has been previously published (12). In the older women, the relationship of MSNA to ASBP and APP were positive so that postmenopausal women with high MSNA have a high ASBP and APP. Conversely, there was no such relationship in young women. See Table 3 for correlation coefficients.

Figure 2.

Linear regression analysis of the relationship between MSNA (burst incidence) and augmentation index (AI_X ; bottom panel), augmented pressure (AP; middle panel) and wasted energy (E_W ; top panel) in postmenopausal ($n = 16$). We compared this to data collected in 23 young women in our laboratory that has been previously published (12). In the older women, the relationship between MSNA and indexes of aortic wave reflection become positive so that postmenopausal women with high MSNA have higher indexes of aortic wave reflection, whereas, these relationships are inversely related in young women. See correlation coefficients in Table 3.

Table 1

Participant demographics

	Young women (n=23)	Older women (n=16)
Age (yrs)	25 ± 1	60 ± 2 *
Body mass (kg)	64 ± 2	67 ± 2
Height (cm)	166 ± 1	165 ± 2
BMI (kg/m ²)	24.2 ± 0.5	24.3 ± 0.6

BMI; body mass index. Mean ±SEM,

*

P<0.05 vs. young women

Table 2

Neural-hemodynamic variables and aortic wave reflection characteristics in 23 young women and 16 postmenopausal women.

Neural/hemodynamic variables	Young women	Older women
Heart rate (beats/min)	64 ± 2	59 ± 2
Stroke volume (ml)	79 ± 3	67 ± 2 *
Cardiac output (l/min)	5.0 ± 0.2	4.1 ± 0.1 *
TPR (mmHg/l/min)	18.6 ± 0.7	24.8 ± 1.1 *
BSBP (mmHg)	127 ± 2	145 ± 5 *
BDBP (mmHg)	71 ± 2	72 ± 2
BMAP (mmHg)	92 ± 2	99 ± 3 *
ASBP (mmHg)	104 ± 2	131 ± 5 *
ADBP (mmHg)	70 ± 2	72 ± 2
APP (mmHg)	34 ± 2	63 ± 4 *
PPA	1.65 ± 0.06	1.19 ± 0.03 *
AI _x (%)	10 ± 2	33.4 ± 2.2 *
AI _x at 75 beats/min (%)	5 ± 2	25.8 ± 2.1 *
AP (mmHg)	4 ± 1	22 ± 3 *
E _w (dynes/cm ² /s)	788 ± 161	4861 ± 605 *
Ejection duration (ms)	342 ± 3	355 ± 4 *
MSNA (bursts/100 heart beats)	25 ± 3	64 ± 3 *
MSNA (bursts/min)	16 ± 2	40 ± 2 *

TPR; total peripheral resistance, BSBP; brachial systolic blood pressure, BDBP; brachial diastolic blood pressure, BMAP; brachial mean arterial pressure, ASBP; aortic SBP, ADBP; aortic DBP, APP; aortic pulse pressure, PPA; pulse pressure amplification, AI_x; augmentation index, AP; augmented pressure, E_w; wasted LV energy, MSNA; muscle sympathetic nerve activity. Mean ± SEM,

* $P < 0.05$ vs. young women. NB: Stroke volume and thus TPR and cardiac output could not be calculated in 2 young women. Mean ± SEM are calculated from 21 young women for these variables.

Table 3

Pearsons correlation coefficients (r) for the relationship of muscle sympathetic nerve activity (MSNA) or total peripheral resistance (TPR) to indexes of aortic wave reflection in young (n=23) and postmenopausal women (n=16).

	ASBP (mmHg)	ADBP (mmHg)	APP (mmHg)	PPA	AI _x (%)	AI _x at 75 beats/min (%)	AP (mmHg)	Ew (dyne/cm ² /s)
MSNA (bursts/100 heart beats)								
Young women	-0.20 (0.36)	0.02 (0.90)	-0.30 (0.16)	0.14 (0.52)	-0.63* (0.01)	-0.57* (0.01)	-0.58* (0.01)	-0.57* (0.01)
Older women	0.63* (0.01)	0.21 (0.73)	0.65* (0.01)	-0.78* (0.01)	0.69* (0.01)	0.56* (0.02)	0.70* (0.01)	0.79* (0.01)
MSNA (bursts/min)								
Young women	-0.21 (0.33)	0.04 (0.89)	-0.39 (0.06)	0.19 (0.36)	-0.63* (0.01)	-0.50* (0.01)	-0.61* (0.01)	-0.60* (0.01)
Older women	0.51* (0.04)	0.20 (0.73)	0.52* (0.04)	-0.58* (0.02)	0.63* (0.01)	0.69* (0.01)	0.65* (0.01)	0.62* (0.01)
TPR (mmHg/l/min)								
Young women (n=21)	0.22 (0.34)	0.34 (0.14)	-0.05 (0.82)	-0.20 (0.38)	-0.08 (0.74)	-0.20 (0.38)	-0.07 (0.76)	-0.08 (0.74)
Older women	0.65* (0.01)	0.65* (0.01)	0.51* (0.04)	-0.52* (0.04)	0.37 (0.16)	0.20 (0.73)	0.48 (0.06)	0.47 (0.07)

See Table 2 for definition of abbreviations. Values are Pearson's correlation coefficients (p-value is bracketed).

* $P < 0.05$.