Aging Enhances Autonomic Support of Blood Pressure in Women

Jill N. Barnes, Emma C. Hart, Timothy B. Curry, Wayne T. Nicholson, John H. Eisenach, B. Gunnar Wallin, Nisha Charkoudian, Michael J. Joyner

Abstract—The autonomic nervous system plays a central role in both acute and chronic blood pressure regulation in humans. The activity of the sympathetic branch of the autonomic nervous system is positively associated with peripheral resistance, an important determinant of mean arterial pressure in men. In contrast, there is no association between sympathetic nerve activity and peripheral resistance in women before menopause, yet a positive association after menopause. We hypothesized that autonomic support of blood pressure is higher after menopause in women. We examined the effect of ganglionic blockade on arterial blood pressure and how this relates to baseline muscle sympathetic nerve activity in 12 young (25±1 years) and 12 older postmenopausal (61±2 years) women. The women were studied before and during autonomic blockade using trimethaphan camsylate. At baseline, muscle sympathetic nerve activity burst frequency and burst incidence were higher in the older women (33±3 versus 15±1 bursts/min; 57±5 versus 25±2 bursts/100 heartbeats, respectively; P<0.05). Muscle sympathetic nerve activity bursts were abolished by trimethaphan within minutes. Older women had a greater decrease in mean arterial pressure (~29±2 versus −9±2 mm Hg; P<0.01) and total peripheral resistance (~10±1 versus −5±1 mm Hg/L per minute; P<0.01) during trimethaphan. Baseline muscle sympathetic nerve activity was associated with the decrease in mean arterial pressure during trimethaphan (r=−0.74; P<0.05). In summary, our results suggest that autonomic support of blood pressure is greater in older women compared with young women and that elevated sympathetic nerve activity in older women contributes importantly to the increased incidence of hypertension after menopause. (Hypertension. 2014;63:00-00.)

Key Words: blood pressure • menopause • sympathetic nerve activity

The autonomic nervous system plays a critical role in both short- and long-term blood pressure regulation and has been implicated in the development of hypertension.1 With advancing age, there is an increase in sympathetic nerve activity in both men and women which is positively associated with the rise in arterial blood pressure.2 In men, sympathetic nerve activity is related to total peripheral resistance (TPR), explaining the neural–hemodynamic link to arterial blood pressure.3,4 Recent work from our laboratory has shown that this relationship also exists in postmenopausal women, but not in young women.5 This strongly suggests that young women regulate blood pressure and vascular resistance differently than young men and older women and has been supported by subsequent studies.6-8

In humans, ganglionic blockade has been used to eliminate the influence of both sympathetic and parasympathetic nerve activity and determine their role in blood pressure regulation.9,10 In this way, the support of blood pressure by the autonomic nervous system (defined as the extent of drop in blood pressure when the system is blocked) can be assessed. Blood pressure decreases during ganglionic blockade are less in young women compared with young men, suggesting sex differences also exist in the degree of autonomic control of blood pressure.11 In men, the magnitude of change in arterial pressure during ganglionic blockade (when the autonomic nervous system is turned off) is dependent on age.9 In contrast to the gradual increase in both sympathetic nerve activity and blood pressure with age in men, women seem to experience a marked shift in neural–hemodynamic control of blood pressure after menopause. Likewise, the incidence of hypertension increases dramatically after menopause,12 indicating that sex hormones play a role in blood pressure regulation. The cumulative effect of the age-related increase in sympathetic nerve activity combined with the reduction in sex hormones after menopause likely contribute to altered blood pressure regulation and increased risk of hypertension in older women.5,13 However, the level of autonomic support of blood pressure, and more specifically the contribution of sympathetic nerve activity to blood pressure at rest, in older women is unknown. Therefore, the purpose of this study was to examine the autonomic support of blood pressure in older postmenopausal women compared with young premenopausal...
women. We hypothesized that ganglionic blockade will result in a greater reduction in arterial pressure in the older women compared with young women. We also hypothesized that the reduction in arterial pressure during ganglionic blockade will be related to tonic sympathetic nervous system activity.

Methods

Participants

A total of 28 healthy women gave written consent and participated in the study. All subjects were healthy, as determined by a review of medical history and brief physical examination, nonsmoking, nonobese (body mass index <28 kg/m²), and normotensive. Potential subjects were recruited from Rochester, MN, and the surrounding area by using classified ads and flyers. Potential subjects were prescreened using questionnaires and medical records. None of the subjects were on any cardiovascular acting medications or had a history of cardiovascular disease or other chronic diseases.

All subjects were either sedentary or recreationally active. The groups were similar in their activity levels (young women exercised 3.3±1.7 sessions/wk and older women exercised 3.3±2.5 sessions/wk). Young women were studied in the early follicular phase of the menstrual cycle or the low hormone phase of oral contraceptive use to minimize the effects of the reproductive hormones on autonomic or cardiovascular function.14 All young women were prescreened using questionnaires and medical records. None had a history of cardiovascular disease or other chronic diseases.

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Experimental Procedures

All of the studies were performed in a CTS Clinical Research Unit at Mayo Clinic where the ambient temperature was controlled between 22°C and 24°C. Subjects arrived at the laboratory after an overnight fast and ≥24 hours without caffeine or vigorous exercise. On arrival, subjects rested supine during instrumentation. After local anesthesia with 2% lidocaine, a 5-cm 20-gauge intravenous catheter was placed in the brachial artery of the nondominant arm, using aseptic technique. 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. An intravenous catheter was placed in the contralateral arm for drug administration. A 3-lead ECG was used for continuous recordings of heart rate. Arterial blood was drawn for the measurement of blood lipoproteins and catecholamine levels.

Multunit muscle sympathetic nerve activity (MSNA) was measured from the right peroneal nerve at the fibular head using insulated tungsten microelectrodes. A muscle sympathetic fascicle was identified when taps on the muscle belly or passive muscle stretch evoked mechanoreceptive impulses, and no afferent neural response was evoked by skin stimuli.15,16 The recorded signal was amplified 80,000-fold, band-pass filtered (700–2000 Hz), rectified, and integrated (resistance-capacitance integrator circuit, time constant 0.1 s) by a nerve traffic analyzer. The signal was amplified, band-pass filtered, rectified, and integrated (662C-4 Nerve Traffic Analysis System, University of Iowa, Iowa City, IA) and then recorded at 250 Hz (WinDaq, DATAQ Instruments, Akron, OH). Sympathetic bursts in the integrated neurogram were identified in the recorded data using an automated analysis program18 that assigns each sympathetic burst to the appropriate cardiac cycle by compensating for latency. The automated analysis was then reviewed by study personnel blinded to the specifics of the study day and corrected manually. In addition to the cardiovascular and neurophysiological criteria included in the automated program,18 a minimum of a 3:1 signal-to-noise ratio was used for burst confirmation. MSNA is reported as bursts/min (burst frequency [BF]) and bursts/100 heartbeats (burst incidence [BI]).

Stroke volume was measured from the brachial artery using Modelflow analysis (BeatScope, Finopres Medical Systems, Amsterdam, The Netherlands) as previously described.19 Briefly, the brachial pressure wave was downloaded onto a personal computer and analyzed offline using data acquisition software (WinDaq, DATAQ Instruments, Akron, OH). Beat-to-beat stroke volume was then calculated using Modelflow which computes this value based on nonlinear pressure–volume, pressure–compliance, and pressure–characteristic impedance equations, incorporating age, sex, height, and body mass.19 Cardiac output was calculated as stroke volume×heart rate, and TPR was calculated as mean arterial pressure (MAP)/cardiac output.

Drug Administration

After a 15-minute baseline period, ganglionic blockade was achieved using incremental intravenous infusion of trimethaphan camsylate (TMP; Cambridge Laboratories, Wallsend, United Kingdom) until subjects demonstrated <5 bpm increase in heart rate during phase II of the Valsalva maneuver.20 TMP blocks neurotransmission at the autonomic ganglia by competing for acetylcholine on the postsynaptic nicotinic receptors. After discontinuation of the study and deinstrumentation, subjects remained in the Clinical Research Unit for ≥2 hours for observation.

Protocol

After the placement of arterial and intravenous catheters, subjects rested supine during instrumentation for microneurography. Once a good quality electrode site for measurement of MSNA was found, 10 minutes of baseline data (cardiac output, arterial pressures, and MSNA) were recorded with the subject resting quietly. After this baseline period, ganglionic blockade was then achieved via infusion of TMP. Once a stable heart rate and blood pressure had been reached, MSNA, arterial pressures, heart rate, and cardiac output were again recorded over 5 minutes.

Data Analysis and Statistics

Data were analyzed statistically using commercially available software (Sigma Stat 12, SPSS Inc., Chicago, IL). Group data are expressed as means±SEM. A 1-way ANOVA was used to determine group differences in demographic data. A multifactorial ANOVA was used to examine whether neural and cardiovascular variables were different in response to TMP within and between each group, with a Bonferroni adjustment for pairwise comparisons. To measure whether there was a relationship of baseline MSNA to cardiovascular variables, linear regression analysis was performed and Pearson correlation coefficients were calculated. The α level was set at 0.05.

Results

Four young women were excluded because of difficulty in obtaining a quality nerve recording or other technical difficulties with study procedures. Therefore, 12 premenopausal and 12 postmenopausal women were included in the data analysis. Subject characteristics are shown in Table 1. Norepinephrine concentrations were higher in older women. Systolic blood pressure measured by an intra-arterial pressure transducer was also higher in older women compared with younger women, although MAP was not different (P=0.14). Importantly, all women in the study were considered normotensive by an automated brachial cuff blood pressure measurement during the screen visit.

Although there were no differences between groups in MAP, TPR was higher, and cardiac output was lower in older
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young Women</th>
<th>Older Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25±1</td>
<td>61±2*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167±2</td>
<td>164±2</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>66±2</td>
<td>64±2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.5±0.6</td>
<td>23.7±0.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>173±8</td>
<td>180±9</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>85±6</td>
<td>103±7</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>69±5</td>
<td>62±3</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>95±11</td>
<td>73±7</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>112±12</td>
<td>191±17*</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>31±8</td>
<td>43±6</td>
</tr>
<tr>
<td>Dopamine, pg/mL</td>
<td>3.4±2.4</td>
<td>2.2±1.5</td>
</tr>
</tbody>
</table>

Data are presented as mean±SEM. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

*P<0.05 vs young women.

women compared with young women (Table 2). In addition, MSNA BI and BF was higher in older women and was associated with norepinephrine concentrations (BI: r=0.60; BF: r=0.68; P<0.01 for both).

Table 2. Sympathetic Nerve Activity and Hemodynamic Responses to Ganglionic Blockade

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young Women</th>
<th>Older Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSNA burst incidence, bursts/100</td>
<td>25±2</td>
<td>57±5*</td>
</tr>
<tr>
<td>heartbeats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSNA burst frequency, bursts/min</td>
<td>15±1</td>
<td>33±3*</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>93±2</td>
<td>98±3</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimephapen</td>
<td>83±3†</td>
<td>68±2*†</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>129±4</td>
<td>145±4*</td>
</tr>
<tr>
<td>Trimephapen</td>
<td>111±4†</td>
<td>95±2*†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>75±2</td>
<td>74±2</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimephapen</td>
<td>69±3</td>
<td>55±2*†</td>
</tr>
<tr>
<td>Total peripheral resistance, mmHg/L per minute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>19.4±1.7</td>
<td>27.8±1.9*</td>
</tr>
<tr>
<td>Trimephapen</td>
<td>14.5±0.9†</td>
<td>17.8±1.2†</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.2±0.5</td>
<td>3.7±0.2*</td>
</tr>
<tr>
<td>Trimephapen</td>
<td>5.9±0.3</td>
<td>4.0±0.2*</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>80±4</td>
<td>63±3*</td>
</tr>
<tr>
<td>Trimephapen</td>
<td>69±2†</td>
<td>60±3*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>64±3</td>
<td>58±2</td>
</tr>
<tr>
<td>Trimephapen</td>
<td>85±3†</td>
<td>66±3*†</td>
</tr>
</tbody>
</table>

Data are presented as mean±SEM. MSNA indicates muscle sympathetic nerve activity.

*P<0.05 vs young women.

†P<0.05 vs control.

The major new findings of the present study are 2-fold. First, ganglionic blockade caused a larger drop in arterial blood pressure in postmenopausal women compared with young women, indicating greater autonomic support of blood pressure in older women. Second, there was a close association between both sympathetic nerve activity and norepinephrine with the magnitude of change in blood pressure. These findings provide novel mechanistic and clinically relevant insight into the regulation of blood pressure in women and changes in this regulation that occur with age and possibly menopause.

There is emerging evidence that sex hormones have major influences on regulation of both blood pressure and blood flow.21 Young men demonstrate a positive relationship between MSNA and TPR and an inverse relationship between MSNA and cardiac output; however, these associations are absent in young women.4 In other words, there is no association between resting sympathetic nerve activity and hemodynamic determinants of blood pressure in young women. This seems to be attributable, in part, to lower α-adrenergic receptor sensitivity in young women and smaller changes in blood pressure during α-adrenergic blockade compared with young men.7,22 In addition, ovariectomy in female rats increases α-adrenergic vasoconstriction, suggesting that...

Discussion

The do...
α-adrenergic sensitivity may be augmented after menopause in older women.23

Lower noradrenergic vasoconstriction in young women may also be attributable to enhanced vasodilating capacity of the β-adrenergic receptors.24 Along these lines, we and others have shown that young women vasoconstrict less to norepinephrine compared with young men.5 Blocking the β-adrenergic receptors with propranolol increases the vasoconstrictor response to norepinephrine only in young women and not in young men.24 During β-adrenergic blockade, a positive association between MSNA and TPR emerges in young women and is more consistent with young men and older women.5 Of note, β-receptor blockade did not alter these associations in young men or older women. This indicates that female sex hormones interact with the β-receptors. Consistent with this idea, a reduction in β-adrenergic sensitivity has been shown in ovariectomized rats.25

In the present study, although both groups demonstrated a significant reduction in blood pressure during ganglionic blockade, the extent of reduction was greater in older women compared with young women. Importantly, the extent of decrease in MAP was inversely associated with measures of sympathetic nervous system activity, including MSNA and plasma norepinephrine and baseline levels of MAP (Figure 3). The fact that both groups fell along the same regression line may seem inconsistent with the idea that older women have greater pressor responses to adrenergic stimulation. However, the only way to directly test this would have been to study two groups with similar levels of resting MSNA. It was not possible to determine whether the decrease in MAP with TMP was similar because the older women had significantly higher baseline MSNA (Table 1).

After menopause, blood pressure regulation in women seems to become more similar to that observed in men, and their risk of hypertension and cardiovascular complications is significantly augmented. In the context of the present results, it is likely that the loss of estrogen and concomitant decrease in vasodilator mechanisms can no longer offset increases in sympathetic nerve activity so there is a net augmentation of vascular resistance. For example, the postmenopausal women in our current study had 43% higher TPR at baseline compared with young women. Previous work indicates that vasopressin is released during ganglionic blockade.26 Potential differences in the vasopressin response between groups were not evaluated in the present study but could also contribute to differences in hemodynamic responses to ganglionic blockade. In

Figure 1. Compressed experimental recording from a representative subject before and during ganglionic blockade. A close-up of the muscle sympathetic nerve activity and blood pressure recording is shown in the box. Note the disappearance of sympathetic bursts during ganglionic blockade with trimethaphan infusion.

Figure 2. A to D, Age-related differences in the magnitude of change in hemodynamic variables between control and trimethaphan. CO indicates cardiac output; HR, heart rate; MAP, mean arterial pressure; and TPR, total peripheral resistance. Means±SEM, *P<0.05 vs young.
postmenopausal women and were able to screen for potential (as detailed in the Methods). Finally, we recruited healthy echocardiography or inhalation of labeled gas concentrations the intra-arterial brachial blood pressure waveform instead of peripheral resistance using established techniques to analyze sion. For similar reasons, we evaluated cardiac output and was different between young and older women during infu-

α-TMP (and limited infusion time), we did not directly assess not study men. Second, because of the limited quantity of quantities left for physiology research. Therefore, we did vous system is no longer produced and there are only small

An interesting observation in this study was that the aver-
gage infusion rate of TMP necessary to achieve ganglionic blockade in young women was double than what was given in older women. In addition, the average infusion rate given to older women (<2 mg/min) was substantially lower than our previous studies using TMP in young adults.27,28 In the study with men by Jones et al.,2 2 mg/min was the starting dose of TMP and it was incrementally increased. This surprising finding may also reflect important age- and menopausal-related changes in blood pressure regulation in older women.

There are several limitations of this study, and the primary issue is that the TMP used to block the autonomic nervous system is no longer produced and there are only small quantities left for physiology research. Therefore, we did not study men. Second, because of the limited quantity of TMP (and limited infusion time), we did not directly assess α-adrenergic sensitivity and cannot determine whether this was different between young and older women during infusion. For similar reasons, we evaluated cardiac output and peripheral resistance using established techniques to analyze the intra-arterial brachial blood pressure waveform instead of echocardiography or inhalation of labeled gas concentrations (as detailed in the Methods). Finally, we recruited healthy postmenopausal women and were able to screen for potential confounding factors. Young women were matched for body mass index for comparison. However, real-world age-related increase in adiposity would likely result in further increases in sympathetic nerve activity in older women. Therefore, it is possible that our findings regarding sympathetic support of blood pressure may be further augmented in older women who are not as lean and healthy as the participants in the present study.

Conclusions
Our results suggest that autonomic support of blood pressure is greater in older women compared with young women and that elevated sympathetic nerve activity in older women may be an important contributor to the increased incidence of hypertension after menopause.

Perspectives
We report here for the first time that ganglionic blockade reduces blood pressure to a greater extent in postmenopausal women compared with younger women, providing further support for targeting the autonomic nervous system to treat hypertension in postmenopausal women. The decrease in blood pressure was directly linked to sympathetic nerve activity, such that women with higher sympathetic nerve activity had greater reductions in blood pressure during ganglionic blockade. In addition, postmenopausal women had augmented peripheral vascular resistance compared with young women. These results point to important changes in mechanisms of blood pressure regulation in women at menopause. Enhanced vasoconstriction, coupled with age-related increases in sympathetic nerve activity, results in a double hit effect on blood pressure, which likely contributes in a major way to the marked increase in risk of hypertension that occurs after menopause.

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Disclosures
None.

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