Sex differences in carotid baroreflex control of arterial blood pressure in humans: relative contribution of cardiac output and total vascular conductance

Areum Kim,1 Shekhar H. Deo,1 Lauro C. Vianna,1 George M. Balanos,3 Doreen Hartwich,3 James P. Fisher,3 and Paul J. Fadel1,2

1Department of Medical Pharmacology and Physiology, 2Dalton Cardiovascular Research Center, University of Missouri, Columbia, Missouri; and 3School of Sport and Exercise Sciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom

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Kim A, Deo SH, Vianna LC, Balanos GM, Hartwich D, Fisher JP, Fadel PJ. Sex differences in carotid baroreflex control of arterial blood pressure in humans: relative contribution of cardiac output and total vascular conductance. Am J Physiol Heart Circ Physiol 301: H2454–H2465, 2011. First published September 30, 2011; doi:10.1152/ajpheart.00772.2011.—It is presently unknown whether there are sex differences in the magnitude of blood pressure (BP) responses to baroreceptor perturbation or if the relative contribution of cardiac output (CO) and total vascular conductance (TVC) to baroreflex-mediated changes in BP differs in young women and men. Since sympathetic vasoconstrictor tone is attenuated in women, we hypothesized that carotid baroreflex-mediated BP responses would be attenuated in women by virtue of a blunted vascular response (i.e., an attenuated TVC response). BP, heart rate (HR), and stroke volume were continuously recorded during the application of 5-s pulses of neck pressure (NP; carotid hypotension) and neck suction (NS; carotid hypertension) ranging from +40 to −80 Torr in women (n = 20, 21 ± 0.5 yr) and men (n = 20, 21 ± 0.4 yr). CO and TVC were calculated on a beat-to-beat basis. Women demonstrated greater depressor responses to NS (e.g., −60 Torr, −17 ± 1% baseline in women vs. −11 ± 1% baseline in men, P < 0.05), which were driven by augmented decreases in HR that, in turn, contributed to larger reductions in CO (−60 Torr, −15 ± 2% baseline in women vs. −6 ± 2% baseline in men, P < 0.05). In contrast, pressor responses to NP were similar in women and men (e.g., +40 Torr, +14 ± 2% baseline in women vs. +10 ± 1% baseline in men, P > 0.05), with TVC being the primary mediating factor in both groups. Our findings indicate that sex differences in the baroreflex control of BP are evident during carotid hypertension but not carotid hypotension. Furthermore, in contrast to our hypothesis, young women exhibited greater BP responses to carotid hypertension by virtue of a greater cardiac responsivenes.

The arterial baroreflex plays an important role in the beat-to-beat regulation of arterial blood pressure (BP). These rapid baroreflex adjustments are mediated by alterations in autonomic neural activity to the heart and vasculature, which modulates cardiac output (CO) and total vascular conductance (TVC), respectively (19, 48). Studies (7, 10) in animals have demonstrated that baroreflex-mediated heart rate (HR) responses are greater in female rodents compared with male rodents. However, limited studies have been performed in humans, and equivocal results have been reported. Indeed, compared with young men, young women have been reported to exhibit similar, increased, or decreased cardiac baroreflex control (1, 8, 13, 59). In addition, the majority of these studies used pharmacological approaches to examine arterial baroreflex function, which do not permit an assessment of BP responses to baroreflex perturbation. Thus, to date, no studies have investigated whether there are sex-related differences in BP responses elicited by the arterial baroreflex.

Previous studies (12, 41, 42) have suggested that alterations in vasomotor activity are the primary means by which the arterial baroreflex regulates BP. In dogs, the pressor response to carotid sinus hypotension via bilateral carotid occlusion was mediated solely by changes in TVC (12). Similarly, human studies (41, 42) have demonstrated that BP responses to carotid baroreflex (CBR) perturbation were predominantly attributable to changes in peripheral vascular tone (i.e., TVC) with a minimal contribution from CO. Of note, these studies recruited predominantly men and were not designed to investigate the potential existence of sex differences in the relative contribution of CO and TVC to BP control by the CBR. Therefore, it remains unknown whether the contribution of CO and TVC in mediating BP responses via the CBR differs between women and men.

The existence of sex differences in baroreflex-mediated changes in TVC responses is highly plausible given that several previous studies have shown marked sex differences in vascular function. Indeed, forearm vasoconstrictor responses to norepinephrine were observed to be blunted in young women compared with men (34, 35). In agreement, recent studies (11, 25, 54) have suggested that young women exhibit lower tonic autonomic nervous system support of arterial BP compared with young men due to their lower basal sympathetic nerve activity and attenuated α-adrenergic sensitivity. Furthermore, a positive relationship between sympathetic nerve activity and total peripheral resistance has been reported in young men but not young women (9, 27). Collectively, these data demonstrate that there is attenuated sympathetically mediated vasoconstriction in women compared with men.

Therefore, we sought to comprehensively examine potential sex differences in the arterial baroreflex control of BP. First, we examined whether the depressor and pressor responses to simulated carotid hypertension and hypotension, respectively, elicited using the variable-pressure neck chamber technique, are different in young women and men. Second, we investigated whether the contribution of CO and TVC to BP responses evoked by CBR perturbation is different in women compared with men. We hypothesized that CBR-mediated BP
responses are attenuated in women due to blunted vascular responses (i.e., an attenuated TVC response).

METHODS

Subjects

For protocol 1 (sex and CBR control of BP), 20 healthy young women (21 ± 0.5 yr) and 20 healthy young men (21 ± 0.4 yr) were recruited from the University of Missouri (Columbia, MO) community. For protocol 2 (validation of Modelflow during CBR perturbation), 10 healthy young subjects (20 ± 1 yr, 3 women and 7 men) were recruited from the University of Birmingham (Birmingham, UK). All subjects were recreationally active, engaging in low- to moderate-intensity (e.g., jogging and cycling) aerobic activities (2–3 days/wk). Any competitive athletes were excluded from the study. All subjects completed a medical health history. No subject had a history or symptoms of cardiovascular, neurologic, or respiratory disorders. All women had a normal menstrual cycle with an average length of 29 ± 2 days, which was identified before the experiments. Young women were studied during the early follicular (3.5 ± 0.3 day) phase of the menstrual cycle, where day 0 is the start of menstruation. All experimental procedures and protocols conformed with the Declaration of Helsinki and were approved by the Health Sciences Institutional Review Board of the University of Missouri (protocol 1) and by the College of Life and Environmental Sciences Ethical Review Committee of the University of Birmingham (protocol 2). Each subject provided written informed consent. Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least 1 day before any experimental sessions. On experimental days, subjects arrived at the laboratory a minimum of 2 h after a light meal.

CBR Function

Using the variable-pressure neck chamber technique, 5-s pulses of +40- and +20-Torr neck pressure (NP) and −20, −40, −60, and −80-Torr neck suction (NS) were applied to sequentially unload (simulated carotid hypotension) and load (simulated carotid hypertension) the carotid baroreceptors, respectively. The application of NP and NS was performed using a malleable lead neck collar fitted around the anterior two-thirds of the neck. Each NP and NS stimulus was delivered 50 ms after the second consecutive R-R interval that did not vary by >50 ms using a customized computer-controlled system (21, 23, 44). Changes in neck collar pressure were generated by a variable pressure source and delivered to the neck collar through large-bore two-way solenoid valves (model 8215B, Asco, Florham Park, NJ). A pressure transducer (model DP45, Validyne Engineering, Northridge, CA) was connected to a port on the collar to accurately quantify the stimulus applied. To minimize respiratory-related modulation of HR, the 5-s pulses of NP and NS were delivered to the carotid sinus during a 12- to 15-s breath hold at end expiration (18). Four to five trials of each level of NP and NS were performed with a minimum of 45 s of recovery allotted between trials to allow all physiological variables to return to prestimulus values.

Familiarization Sessions

All subjects were familiarized with the study equipment and procedures before any experimental visits. During familiarization sessions, subjects were screened to identify the location of the carotid sinus bifurcation using Doppler ultrasound to ensure that the neck collar fully enclosed the carotid sinuses. Indeed, although transmission to the carotid sinus has been shown to be near complete, there is variability in the location of the carotid sinuses that requires consideration (20, 46). Appropriate neck chamber placement was determined by fitting the subjects based on carotid sinus location and observed neck size and then performing resting trials of NP and NS to determine directionally appropriate and consistent cardiovascular responses. Two sessions were typically performed to assure subject familiarity and consistent responses to NP and NS.

Protocols

Protocol 1: sex and CBR control of BP. To determine whether sex influences CBR control of BP, beat-to-beat changes in BP and HR were assessed during the application of NP and NS in young women and men.

EXPERIMENTAL MEASUREMENTS. HR was continuously monitored using a standard lead II surface ECG (Quinton Q710 Foremost Equipment, Rochester, NY). Beat-to-beat BP was measured using photoplethysmography obtained from the left middle finger positioned at the level of the right atrium in the midaxillary line (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). Finometer measurements were validated with absolute arterial BP measurements obtained by an automated sphygmomanometer (SunTech, Medical Instruments, Raleigh, NC). Before Finometer recordings were obtained, diastolic BP of the Finometer was matched with diastolic BP measurements obtained from the brachial artery of the right arm by the SunTech device. Respiratory movements were monitored using a strain-gauge pneumobelt placed around the abdomen. Stroke volume (SV) was estimated from the arterial BP waveform using the Modelflow method through Beatscope (TNO-TPD, Biomedical Instrumentation, Amsterdam, The Netherlands), which incorporates age, sex, weight, and height, as previously described in detail (29, 30, 62). Briefly, Modelflow is a nonlinear three-element model that uses the arterial input impedance (including continuous correction for variations in the diameter), the compliance of the aorta, and total peripheral resistance to describe the relationship between aortic flow and pressure and thus compute SV (62). CO was calculated from beat-to-beat HR and SV (CO = HR × SV), and TVC was calculated as the ratio between CO and mean arterial pressure (MAP). In addition, the cardiac index (CI) was calculated from beat-to-beat CO divided by body surface area (body surface area (in m²) = 0.20247 × height (in m)0.725 × weight (in kg)0.425) (16), and the TVC index (TVCI) was calculated from beat-to-beat TVC divided by body surface area. We reasoned that the use of CI and TVCI were important because they take into consideration differences in body size when comparing women and men (31). The ECG signal and BP waveform were sampled at 1,000 Hz (Powerlab, AD Instruments, Bella Vista, New South Wales, Australia), and beat-to-beat values of HR, systolic BP, diastolic BP, and MAP were stored for offline analysis (Chart version 5.2, AD Instruments).

EXPERIMENTAL PROCEDURES. All subjects were seated in a semi-recumbent position throughout the experimental protocol. After the instrumentation for BP and HR measurements, 5 min of quiet resting baseline data were collected. After the resting baseline, subjects were fitted with the neck collar for the application of NP and NS. CBR-mediated MAP and HR responses were determined by applying random-ordered single 5-s pulses of NP and NS ranging from +40 to −80 Torr (i.e., +40, +20, −20, −40, −60, and −80 Torr), as described in detail above.

Protocol 2: validation of Modelflow during CBR perturbation. To determine whether CO, CI, and SV changes to NP and NS measured via Modelflow were consistent with direct measures obtained using Doppler echocardiography, beat-to-beat SV was measured using Doppler echocardiography and compared with those measurements simultaneously obtained with the Modelflow method.

EXPERIMENTAL MEASUREMENTS. Subjects were instrumented for measurements of HR and BP as described in protocol 1. In addition, Doppler echocardiography (Philips Sonos 7500) was used to identify beat-to-beat changes in flow through the aortic valve during systole while an apical five-chamber view of the heart was obtained with a two-dimensional cardiac transducer (1–3 MHz) (38). The velocity profile of the aortic flow was obtained in pulsed-wave spectral mode.

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Predicted change in MAP\textsubscript{TVC} = MAP\textsubscript{TVC} - MAP\textsubscript{control}

Actual change in MAP = MAP - MAP\textsubscript{control}

Percent contribution of CO = (predicted change in MAP\textsubscript{CO}) / (actual change in MAP) × 100

Percent contribution of TVC = (predicted change in MAP\textsubscript{TVC}) / (actual change in MAP) × 100

where MAP\textsubscript{CO} is the MAP response to CBR stimulation due to CO alone, MAP\textsubscript{TVC} is the MAP response to CBR stimulation due to TVC alone, MAP\textsubscript{control} is the MAP value before NP or NS, CO\textsubscript{control} is the CO value before NP or NS, and TVC\textsubscript{control} is the TVC value before NP or NS.

HR variability analyses. A previous study (43) has demonstrated that parasympathetic nerve activity is a primary factor in mediating HR responses via the CBR. Thus, in an attempt to understand if differences in cardiac parasympathetic control may contribute to any sex differences in the CBR control of HR, indexes of cardiac autonomic control were derived using time- and frequency-domain analysis of spontaneous oscillations in HR (60). Time-domain analysis of HR variability (HRV) was performed using the square root of the mean of the sum of squares of successive differences in the R-R interval (rMSSD), which is recommended for the estimation of short-term high-frequency (HF) variability of HR. Frequency-domain analysis of HRV was performed using fast Fourier transformation, and power spectral density calculated at the HF range (0.15–0.4 Hz) and low-frequency (LF) range (0.04–0.15 Hz) (60). It is generally accepted that HF power predominantly represents cardiac parasympathetic tone. The ratio between LF and HF has been proposed as a measure of the balance between the cardiac and sympathetic control of the heart, but this still remains questionable (61). Thus, in the present study, indexes of cardiac parasympathetic tone were principally used (i.e., rMSSD and HF power). However, for completeness, LF power and the LF-to-HF ratio are also provided.

Beat-to-beat CO analyses. For protocol 2, beat-to-beat changes in SV were simultaneously obtained with Modelflow and Doppler echocardiography and matched with the responses of HR to estimate CO. Although previous studies (30, 57, 62) have shown that Modelflow is able to track changes in SV and estimate CO during various experimental protocols, we wanted to specifically address the validity of this technique during the application of NP and NS in a beat-to-beat manner. Therefore, the intraclass coefficient correlation was calculated to assess the intertechnique variability. In addition, beat-to-beat changes in CO (and CI) to NP and NS obtained using Modelflow were plotted against changes in CO (and CI) obtained using Doppler echocardiography. A line of identity as well as a least-squares fit were drawn to verify any type of systematic difference between the two methods.

Statistical Analysis

All data are presented as means ± SE. Statistical analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL) and Statistical Package for the Social Sciences (SPSS). For group comparisons of the cardiovascular responses to NP, 2 × 2 (sex × level) repeated-measures ANOVA was performed, whereas for NS, 2 × 4 (sex × level) repeated-measures ANOVA was used. A Student-Newman-Keuls test was used post hoc to investigate main effects and interactions. When appropriate, an unpaired t-test was used to compare groups. Statistical significance was set at P < 0.05.

RESULTS

Protocol 1: Sex and CBR Control of BP

Baseline characteristics. Young women and men had similar body mass indexes; however, young women had lower...
body weights and body surface areas (Table 1). Resting HR, diastolic BP, and CI were similar between groups, whereas systolic BP, MAP, pulse pressure, SV, CO, TVC, and TVCI were significantly lower in young women (P < 0.05). No group differences were seen in the time-domain measure of HRV (rMSSD; Table 2). Although a significantly greater total spectral power was observed in men, none of the other frequency-domain indexes of HRV were different between groups.

**CBR control of BP.** Figure 1A shows peak MAP responses to the range of NP and NS stimuli in young women and men presented as absolute changes. Decreases in MAP in response to simulated carotid hypertension (i.e., NS) were significantly greater in young women compared with young men. Similar results were found when the data were expressed as percent changes (sex: P = 0.003, level: P < 0.001, interaction, P < 0.001; e.g., −60 Torr, −17 ± 1% baseline in women vs. −11 ± 1% baseline in men, P < 0.05). The magnitude of the difference between women and men in the fall in MAP with NS was less marked during low-level NS (−20 Torr) than during higher levels of NS (e.g., −80 Torr). In contrast, peak MAP responses to simulated carotid hypotension (i.e., NP) were not different between groups expressed as either absolute changes (Fig. 1A) or percent changes (sex: P = 0.095, level: P < 0.001, interaction: P = 0.664; e.g., +40 Torr, +14 ± 2% baseline in women vs. +10 ± 1% baseline in men).

![Fig. 1. Summary data showing peak mean arterial pressure (MAP; A) and heart rate (HR; in beats/min; bpm) responses elicited by acute carotid baroreceptor unloading (neck pressure (NP), +40 and +20 Torr) and loading [neck suction (NS), −20, −40, −60, and −80 Torr] in young women and men. Values are means ± SE. *Significantly different from women (P < 0.05).](http://ajpheart.physiology.org/)

**CBR control of HR.** Peak HR responses to NP and NS in young women and men presented as absolute changes are shown in Fig. 1B. Bradycardic responses to simulated carotid hypertension were significantly greater in young women compared with young men. Similar results were found when the data were expressed as percent changes (sex: P = 0.002, level: P < 0.001, interaction, P < 0.001; e.g., −60 Torr, −28 ± 2% baseline in women vs. −17 ± 2% baseline in men, P < 0.05). The magnitude of the difference between women and men in the bradycardic response to NS was less marked during low-level NS (−20 Torr) than during higher levels of NS (e.g., −80 Torr). No significant sex differences were observed in the magnitude of the peak HR responses to simulated carotid hypotension expressed as either absolute changes (Fig. 1B) or percent changes (sex: P = 0.620, level: P < 0.001, interaction: P = 0.258; e.g., +40 Torr, +15 ± 1% baseline in women vs. +15 ± 1% baseline in men).

**CBR latency of MAP and HR.** Original records showing the temporal pattern of beat-to-beat MAP and HR responses to NS (−60 Torr) and NP (+40 Torr) in young women and men are shown in Figs. 2 and 3, respectively. The group average time to peak MAP in response to NS was significantly shorter in young women compared with young men (+4.7 ± 0.3 s in women vs. +5.9 ± 0.3 s in men, P < 0.05), whereas the time to peak HR was not different between groups (+1.8 ± 0.2 s in women vs. +1.9 ± 0.2 s in men, P > 0.05). The time to peak

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**Table 1. Subject characteristics**

<table>
<thead>
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<th></th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>21 ± 0.5</td>
<td>21 ± 0.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61 ± 2</td>
<td>73 ± 2*</td>
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<tr>
<td>Height, cm</td>
<td>166 ± 1</td>
<td>178 ± 1*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22 ± 1</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.68 ± 0.03</td>
<td>1.90 ± 0.02*</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>66 ± 2</td>
<td>63 ± 2</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>109 ± 2</td>
<td>119 ± 2*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>66 ± 2</td>
<td>68 ± 1</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>80 ± 2</td>
<td>85 ± 1*</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>43 ± 2</td>
<td>51 ± 2*</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>73 ± 2</td>
<td>98 ± 4*</td>
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<tr>
<td>Cardiac output, l/min</td>
<td>4.8 ± 0.2</td>
<td>6.1 ± 0.2*</td>
</tr>
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<td>Cardiac index, 1 min−1m−2</td>
<td>2.9 ± 0.1</td>
<td>3.2 ± 0.1</td>
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<tr>
<td>Total vascular conductance, lmin−1mmHg−1</td>
<td>0.056 ± 0.002</td>
<td>0.075 ± 0.003*</td>
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<tr>
<td>Total vascular conductance index, lmin−1mmHg−1m−2</td>
<td>0.033 ± 0.001</td>
<td>0.039 ± 0.002*</td>
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</table>

Values are means ± SE. *Significantly different from women (P < 0.05).

**Table 2. Time- and frequency-domain indexes of heart rate variability**

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time domain</td>
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<tr>
<td>rMSSD, ms</td>
<td>53 ± 8</td>
<td>65 ± 10</td>
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<tr>
<td>Frequency domain</td>
<td></td>
<td></td>
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<tr>
<td>LF (0.04-0.15 Hz), ms²</td>
<td>1039 ± 477</td>
<td>2603 ± 1262</td>
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<tr>
<td>HF (0.15-0.4 Hz), ms²</td>
<td>947 ± 287</td>
<td>1314 ± 419</td>
</tr>
<tr>
<td>Total power, ms²</td>
<td>2539 ± 694</td>
<td>5065 ± 1507*</td>
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<tr>
<td>LF, NU</td>
<td>0.49 ± 0.08</td>
<td>0.60 ± 0.07</td>
</tr>
<tr>
<td>HF, NU</td>
<td>0.51 ± 0.08</td>
<td>0.40 ± 0.07</td>
</tr>
<tr>
<td>LF-to-HF ratio, NU</td>
<td>2.55 ± 1.73</td>
<td>2.90 ± 1.03</td>
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</table>

Values are means ± SE. rMSSD, square root of the mean of the sum of the squares of successive differences in the R-R interval; LF, low-frequency power spectral density; HF, high-frequency power spectral density, NU; normalized units. *Significantly different from women (P < 0.05).
MAP in response to NP was also significantly shorter in young women compared with young men (5.5 ± 0.2 s in women vs. 6.2 ± 0.2 s in men, \( P < 0.05 \)), with no differences in time to peak HR between women and men (4.2 ± 0.2 s in women vs. 4.3 ± 0.2 s in men, \( P > 0.05 \)).

**CBR control of TVC and CO.** Figure 4 shows changes in TVC, CO, and SV to NP and NS at the time of the peak MAP response in young women and men presented as absolute changes. Whereas in young men there was a noticeable increase in TVC in response to simulated carotid hypertension, young women exhibited no change or a small reduction in TVC with NS. Similar results for NS were found when the TVC data were expressed as percent changes (sex: \( P = 0.023 \), level: \( P = 0.217 \), interaction: \( P = 0.150 \); e.g., 60 Torr, 6 ± 2% baseline in women vs. 6 ± 2% baseline in men). In contrast, the fall in CO with NS was significantly greater in young women.

**CBR control of TVC and CO.** Figure 4 shows changes in TVC, CO, and SV to NP and NS at the time of the peak MAP response in young women and men presented as absolute changes. Whereas in young men there was a noticeable increase in TVC in response to simulated carotid hypertension, young women exhibited no change or a small reduction in TVC with NS. Similar results for NS were found when the TVC data were expressed as percent changes (sex: \( P = 0.023 \), level: \( P = 0.217 \), interaction: \( P = 0.150 \); e.g., 60 Torr, 6 ± 2% baseline in women vs. 6 ± 2% baseline in men). In contrast, the fall in CO with NS was significantly greater in young women.
The magnitude of the TVC and CO response to NP was not different between groups when presented as absolute changes (Fig. 4) or percent changes (sex: $P = 0.414$, level: $P < 0.001$, interaction: $P = 0.406$ for TVC; and sex: $P = 0.326$, level: $P = 0.001$, interaction: $P = 0.407$ for CO). NP produced a small fall in SV, which tended to be greater in young men than young women (Fig. 4C). Group and individual summary data showing the percent changes in TVC and CO at the time of the peak MAP response to simulated carotid hypotension are shown in Fig. 6. As shown by the individual summary data and box plots, there were no significant trends in TVC (Fig. 6A) or CO (Fig. 6B) responses in either young women or young men. Furthermore, no sex differences were observed in the percent contribution of TVC or CO to the peak MAP response to NP (Fig. 6C). Of note, CI and TVC1 responses to NP and NS were similar to those described for CO and TVC, respectively.

The slope of the relationship between percent changes in TVC and estimated carotid sinus pressure (MAP minus chamber pressure) across the range of neck chamber pressures was significantly less in young women compared with young men ($+0.051 \pm 0.022$ in women vs. $+0.140 \pm 0.029$ in men, $P = 0.022$). In contrast, the slope of the relationship between percent changes in CO and estimated carotid sinus pressure was significantly greater in young women compared with young men ($-0.200 \pm 0.029$ in women vs. $-0.092 \pm 0.022$ in men, $P = 0.005$).

**Protocol 2: Validation of Modelflow During CBR Perturbation**

Subjects had similar baseline characteristics for protocol 2 (age: $20 \pm 1$ yr, weight: $66 \pm 3$ kg, height: $175 \pm 3$ cm) as those in protocol 1. Figure 7 shows the beat-to-beat CO responses to carotid hypertension (A) and hypotension (B) derived simultaneously by Doppler echocardiography and Modelflow. No significant differences were observed between methods ($P > 0.05$). Figure 7C shows that CO values simultaneously derived from Modelflow ($x$-axis) and Doppler echocardiography ($x$-axis) showed good agreement and were closely associated with the line of identity. The least-squares fit supported this agreement. This interpretation was further supported by an intraclass coefficient correlation of 0.947 (95% confidence interval of 0.918–0.965, $P < 0.001$). Similar results were obtained from a comparison of CI values simultaneously determined with Modelflow and Doppler echocardiography (intraclass coefficient correlation of 0.933, 95% confidence interval of 0.910–0.951, $P < 0.001$).

**DISCUSSION**

To our knowledge, this is the first study to assess whether there are sex differences in depressor and pressor responses to baroreceptor perturbations and to determine the relative contribution of the heart (CO) and peripheral vasculature (TVC) to these BP responses. The novel findings of our study are threefold. First, baroreflex-mediated depressor responses to carotid hypertension were greater in young women compared with young men, whereas baroreflex-mediated pressor responses to carotid hypotension were similar between sexes. Second, in young women, BP responses to carotid hypertension were predominantly attributable to a change in CO, whereas in young men, a change in TVC was the major

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**Fig. 4.** Summary data showing peak TVC (A), CO (B), and stroke volume (SV; C) responses at the time of the peak MAP response elicited by acute carotid baroreceptor unloading (NP, $+40$ and $+20$ Torr) and loading (NS, $-20$, $-40$, $-60$, and $-80$ Torr) in young women and men. Values are means $\pm$ SE. *Significantly different from women ($P < 0.05$).
contributor to the change in BP. Finally, in response to carotid hypotension, the relative contribution of TVC and CO to the BP response was similar in young women and men. Overall, sex differences in the baroreflex control of BP appear to be more evident during carotid hypertension than hypotension. In contrast to our original hypothesis, young women exhibited greater BP responses to carotid hypertension due to a greater cardiac responsiveness.

Previous studies (12, 41, 42) have demonstrated that CBR-mediated BP responses were primarily due to peripheral vascular changes (i.e., TVC) with a minimal cardiac contribution. As mentioned, these studies recruited predominantly men and were not designed to address potential sex differences or differences in the responses to simulated carotid hypertension and hypotension. Our findings indicate that young women exhibit minimal changes in TVC to stimulation of the carotid baroreceptors. Surprisingly, despite such small changes in TVC, young women had greater CBR-mediated depressor responses than young men. Thus, greater reductions in BP to simulated carotid hypertension in young women appear to be driven by a larger decrease in CO. Although the mechanism(s) underlying these sex differences is not clear, the lack of an increase in TVC to NS is in line with previous studies (11, 25, 34, 35, 54). Indeed, investigators have shown that young women have lower levels of muscle sympathetic nerve activity (27, 40, 55) and that systemic blockade of the sympathetic nervous system causes less of a decrease in BP in young women (11, 54), indicative of a lower tonic sympathetic support of BP in young women compared with young men. Our observations support and extend these findings by showing that compared with young men, young women have a greater reliance

Fig. 5. Group (left) and individual (right) summary data showing percent changes in TVC (A) and CO (B) at the time of the peak MAP response elicited by acute carotid baroreceptor loading (NS, -60 Torr). C: relative contribution of TVC and CO to the depressor response elicited by carotid baroreceptor loading (NS, -60 Torr). Values are means ± SE. * Significantly different from women ($P < 0.05$).
on CO than on TVC for the moment-to-moment control of BP via the arterial baroreflex.

In the present study, the greater depressor responses to simulated carotid hypertension in young women appeared to be due to a larger reduction in CO, which was driven by an augmented decrease in HR, with a minimal change in SV. The reason for the greater reflex bradycardia in young women is unclear. Although several previous studies (3, 36, 51, 52) have suggested that young women have a higher parasympathetic tone than men of a similar age, this has not been a universal finding (47, 56). In addition, we did not observe a difference in time- or frequency-domain estimates of resting parasympathetic tone in our study. Interestingly, previous studies have reported that women exhibit greater cardiac responses to laboratory stressors compared with men (e.g., cold pressor test) (2, 39) and indicated that females have greater parasympathetic responsiveness, whereas males exhibit greater sympathetic responsiveness (14, 17). Du et al. (17) reported that female rats exhibit more marked parasympathetic control of HR by virtue of a greater acetylcholine release in response to vagal nerve stimulation and that this causes a greater reduction in HR followed by an augmented fall in BP. The greater decrease in HR and larger and more rapid reduction in BP (i.e., reduced time to peak latency) to similar levels of hypertensive stimuli (NS) we observed in young women compared with young men broadly supports these findings in rats.

In contrast to the notable sex differences in the cardiovascular responses to carotid hypertension, no differences were noted between young women and men in the responses of MAP, HR, CO, or TVC to carotid hypotension. These obser-
vations were somewhat unexpected. Previously, it has been suggested that women have reduced sympathetic vasomotor regulation of BP (6, 9, 27) and lower α-adrenergic sensitivity and reduced vasoconstrictor responses to α-adrenergic agonists (25, 34, 35, 54); however, our results do not support these findings. One factor that might contribute to this discrepancy is that we assessed beat-to-beat changes over a short period (i.e., 10 s), whereas previous studies (25, 34, 35, 54) examined time-averaged responses from longer-term steady-state periods ranging from 30 s to 8 min after pharmacological interventions. In addition, some consideration of the size of the study sample is warranted. Based on pilot studies from our laboratory, adequate sample sizes were calculated before the study was undertaken by applying a desired power of 0.80 and an error of 5%. For NS, an effect size of $d = 1.15$ was used, and the minimum sample size was determined to be 16 subjects in each group. For NP responses, however, 328 subjects were needed in each group based on an effect size of $d = 0.22$. Given the scope of the present study, we felt that this large number was unrealistic to obtain. However, considering the potential for statistical type error 1, caution should be taken when interpreting the trends seen in the responses to NP. Although a tendency for a smaller change in TVC in response to NP was noted in young women, this does not explain why the pressor response to carotid hypotension was slightly (but nonsignificantly) greater in young women.

Traditionally, arterial baroreflex function in humans has been determined using a pharmacological approach, such as the modified Oxford technique (i.e., phenylephrine and sodium nitroprusside). The use of drugs to elicit BP changes by constriction and dilatation of the vasculature means that only reflex changes in HR and sympathetic nerve activity may be determined (1, 8, 13, 59). An advantage of using the variable-pressure neck chamber technique in our study is that it permits the evaluation of BP responses. Moreover, with this approach, it is possible to simultaneously evaluate the dynamic changes in TVC and CO in response to acute carotid baroreceptor perturbation and ascertain their relative contribution to the resultant BP response to both simulated hypotension and hypertension. Importantly, most studies (13, 27) investigating sex differences in arterial baroreflex control have not separately considered the reflex responses to baroreceptor unloading and loading. This was a particular advantage of the present study, as although no sex differences were observed in the cardiovascular response to carotid hypotension, clear sex differences were present in response to carotid hypertension. These findings highlight the importance of separately considering the responses to falls and rises in BP when evaluating baroreflex function, as recently suggested (58).

There is accumulating evidence to suggest that there are important sex differences in cardiovascular regulation in both health and disease. Indeed, the incidence of orthostatic hypotension is believed to be greater in young women, whereas the severity and incidence of hypertension are lower in premenopausal women (15, 53). Recently, Joyner and colleagues (9, 28) have suggested that in contrast to men, women do not show a relationship between muscle sympathetic nerve activity and total peripheral resistance, supporting the notion that there are inherent differences in BP regulation between the sexes. Interestingly, our data indicate that young women and men have similar cardiovascular responses to carotid hypotension, perhaps indicating that differences in CBR sensitivity do not underlie the sex differences in the prevalence of orthostatic intolerance (24, 26, 63). However, we found that young women
have augmented CO and BP responses to carotid hypertension. Given the potential significance of baroreceptor activity for longer-term BP regulation (37), one might speculate that this contributes to the lower BP often observed in premenopausal women and serves as a beneficial protective mechanism (40). Additional studies are required to determine if the sex-related differences we observed in the CBR control of BP are mediated by alterations in mechanical transduction, afferent signaling, central integration, autonomic efferent activity, or neural-vascular transduction.

We principally obtained measurements of SV and CO using the Modelflow method, which has previously been shown to accurately track changes in SV and estimate CO during various experimental laboratory-based perturbations (30, 57, 62). In the present study, we observed that CO responses to NP and NS obtained with Modelflow were in close agreement with those obtained using Doppler echocardiography. However, we did not examine whether there were sex differences in the agreement between the Modelflow method and the Doppler echocardiography technique due to the small number of women in this protocol (n = 3). Nevertheless, limited measurement errors were observed in those women that were measured using Doppler echocardiography. Thus, Modelflow was deemed to be valid, and somewhat preferable to Doppler echocardiography, because obtaining an optimal apical five-chamber view of the heart was technically challenging in some women due the influence of anatomy on probe positioning. However, it should be made clear that our measurements were only made in young healthy volunteers under well-controlled and transient conditions. Whether these findings are applicable to patients with cardiovascular disease or during other experimental interventions remains unknown. Importantly, in agreement with a previous study (41), carotid-baroreceptor perturbation induced minimal changes in SV from prestimulus levels in both young women and men. Given this, we reasoned that SV does not play a primary role in the modulation of BP responses via the arterial baroreflex.

Potential limitations of the present study require consideration. First, blood flow was not directly measured, and, since it can strongly influence venous return and, thus, CO, it is unclear how blood volume differences in women and men affected the present results. However, minimal CBR-mediated changes in SV were observed in both young women and men. Second, the brevity of the NP and NS stimuli used may not allow for full CBR-mediated responses to be obtained. However, the 5-s stimuli were necessary to selectively activate carotid baroreceptors without counteraction from aortic and cardiopulmonary baroreceptors (20, 45, 49). Furthermore, both women and men exhibited peak and nadir BP responses to NP and NS, respectively, that occurred within 3–8 s, which was well within the timeframe studied (i.e., breath hold still present). Importantly, this BP response profile is consistent with the findings of numerous studies and is in line with the muscle sympathetic nerve activity and peak vascular responses to NP and NS previously reported in young men (21, 22, 32, 50). Nevertheless, we recognize that the results of the present study are specific to the 5-s stimuli used. In addition, the potential for sex-related differences in extracarotid baroreceptor populations remains to be determined.

In summary, we found that women exhibited greater baro-reflex-mediated depressor responses to carotid hypertension. The mechanism for such responses appeared to be a larger reduction in CO, which was driven by an augmented brady-cardiac response. In contrast, baroreflex-mediated pressor responses to carotid hypotension appeared similar between young women and men, and vascular changes were a primary mediating factor in both sexes. Overall, our findings indicate that sex differences in the baroreflex control of BP appear to be more evident during carotid hypertension than hypotension and that young women exhibit greater BP responses to carotid hypertension by virtue of a greater cardiac responsiveness.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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