Baroreflex Regulation of Heart Rate and Sympathetic Vasomotor Tone in Women and Men

Jens Tank, Andre Diedrich, Elke Szczech, Friedrich C. Luft, Jens Jordan

Abstract—Gender has been reported to influence baroreflex heart rate regulation and baroreflex blood pressure buffering. We tested the hypothesis that gender influences baroreflex regulation of heart rate and sympathetic vasomotor tone. We recruited 32 normal-weight healthy subjects (17 men and 15 women). ECGs for heart rate, brachial and finger blood pressure, and muscle sympathetic nerve activity (MSNA) were measured. Baroreflex heart rate and MSNA regulation were assessed using incremental phenylephrine and nitroprusside infusions. Baseline blood pressure was similar in men and women. MSNA was 21±2.5 bursts/min in women and 19±2.8 bursts/min in men (NS). The gain of the baroreflex MSNA curves was similar in women and men (−1.9±0.2 bursts/min per mm Hg in men and −2.0±0.3 bursts/min per mm Hg in women). Baroreflex gain for heart rate regulation was 17±3.2 ms/mm Hg in women and 19±1.9 ms/mm Hg in men (NS). We conclude that baroreflex gains for heart rate and sympathetic MSNA regulation are similar in women and men. However, the probability for congruence between men and women in terms of the MSNA baroreflex curves was 0.06% for burst rate, 0.4% for burst incidence, and 0.01% for burst area. In women, the MSNA baroreflex curve may be shifted to slightly lower blood pressure such that at a given blood pressure MSNA tends to be lower. (Hypertension. 2005;45:1159-1164.)

Key Words: autonomic nervous system ■ baroreflex ■ gender ■ nervous system, sympathetic

The autonomic nervous system influences blood pressure and heart rate through adjustments in parasympathetic and sympathetic activity. Parasympathetic and sympathetic activities are tightly regulated through baroreflex mechanisms. Therefore, baroreflexes have a pivotal role in short-term cardiovascular regulation and buffer-excessive blood pressure swings. Among numerous other variables, baroreflexes are also involved in long-term blood pressure maintenance.5 Even when overall blood pressure regulation is functioning properly, the balance between baroreflex regulation of heart rate and vascular tone may be perturbed. Imbalance between sympathetic activation of the heart and the vasculature has been described in heart failure patients, postural tachycardia syndrome patients, and in healthy subjects treated with norepinephrine transporter inhibitors.9,10 Factors influencing baroreflex function may have an important bearing on human cardiovascular disease. Gender may be such a variable. Previous studies suggest that baroreflex blood pressure buffering is less effective in women than in men.11 The balance between baroreflex-mediated heart rate and muscle sympathetic nerve activity (MSNA) changes may also be influenced by gender. The idea is supported by the observation that resting sympathetic vasomotor tone tends to be decreased in women, whereas resting heart rate is increased.14-16 Furthermore, with standing, women showed an exaggerated heart rate and an attenuated sympathetic vasomotor response.17 Moreover, previous studies suggested that baroreflex heart rate regulation may be different between men and women.18-20 Finally, estrogen influences baroreflex regulation in humans21-23 and in animals.24 Therefore, we tested the hypothesis that gender influences baroreflex regulation of heart rate and sympathetic vasomotor tone.

Methods

Subjects
We recruited 32 normal-weight healthy subjects (17 men and 15 women) through local advertisements (Table 1). Both groups were matched for age. Men were heavier and taller than women. Body mass index was slightly greater in men compared with women. Eight women ingested birth control pills. Otherwise, the subjects received no medications. Competitive athletes were excluded from the study. Written informed consent was obtained before study entry. All studies were approved by our institutional review board.

Instrumentation
ECG and beat-by-beat blood pressure (Finapres; Ohmeda) were measured continuously (Cardioscreen; Medis GmbH). Brachial arterial blood pressure (Dinamap; Critikon) was determined. MSNA was recorded from the right peroneal nerve (MSNA unit, Biomedical Engineering Department, University of Iowa, Iowa City). A unipolar tungsten electrode ( uninsulated tip diameter of 1 to 5 μm; shaft diameter of 200 μm) was inserted into the muscle nerve fascicles of...
The peroneal nerve at the fibular head for multiunit recordings. Nerve activity was amplified with a total gain of 100 000, bandpass filtered (0.7 to 2 kHz), full-wave rectified, and integrated. MSNA recordings were accepted as adequate according to the following criteria: (1) pulse synchrony; (2) facilitation during Valsalva straining, and suppression during the hypertensive overshoot after release; (3) increases in response to breath holding; and (4) insensitivity to emotional stimuli.

Protocol
Testing was conducted with the subjects in the supine position. After instrumentation, subjects rested for at least 20 minutes to achieve a stable baseline. Then, resting heart rate, blood pressure, and MSNA were recorded. After the baseline recording, incremental infusions of sodium nitroprusside and phenylephrine hydrochloride (0.2, 0.4, 0.8, and 1.6 µg/kg per minute over 5 minutes each) were given. Infusions were stopped after the maximum dose had been given or after systolic blood pressure had changed by ≥15 mm Hg. Subjects rested for 20 minutes before the second drug was infused to achieve another stable baseline. At the end of this period, resting heart rate, blood pressure, and MSNA for the baroreflex plots were recorded.

Data Acquisition and Analysis
Data were analog-to-digital converted at 500 Hz using Windaq Pro+ software (Dataq Instruments). R-R intervals, diastolic blood pressure, systolic blood pressure values, and sympathetic bursts were defined off-line for the complete records using a program written by one of the authors (A.D.) that is based on PV-wave software (Visual Numerics, Inc). MSNA bursts were identified after filtering the signal and defining the baseline according to following criteria: (1) signal-to-noise ratio (set to 2.5); (2) tolerance limits of the skewness of the rising and falling parts of the bursts; (3) latency limit after the previous (1 removed) electrocardiographic R-wave (1.0 to 1.6 s); (4) burst width limit (duration <0.2 s =artifact; duration >0.8 s =skin sympathetic nerve activity or afferent activity); and (5) no preceding premature beats. The number of bursts per minute (burst frequency) and the number of bursts per 100 heart beats (burst incidence) were quantified. We also calculated the mean area under the MSNA bursts per minute.

Spectral Analysis and Baroreflex Sensitivity
We calculated individual pharmacological baroreflex sensitivities by plotting changes in R-R interval or MSNA against changes in systolic blood pressure. The maximal slope of the linear part of the resulting baroreflex curve was analyzed by linear regression analysis. Heart rate and blood pressure variability were determined in the time and frequency domain by using spectral analysis, cross-spectral analysis, and the transfer function between R-R intervals and systolic blood pressure as described previously. Briefly, beat-to-beat series were interpolated and resampled at 4 Hz. The power spectra density was estimated by the Welch method, with zero padding, linear trend elimination, and a 50% overlapped Hanning window. Low-frequency (LF) power (0.04 to 0.15 Hz), high-frequency (HF) power (0.15 to 0.4 Hz), and the LF/HF ratio were calculated. HF power is considered to mainly reflect parasympathetic heart rate control. LF power reflects sympathetic and parasympathetic heart rate control. The LF/HF has been suggested by some investigators to reflect sympathetic-vagal balance of heart rate control.

Spontaneous baroreflex sensitivity (BRS) was calculated using the sequence technique and the cross-spectral analysis as described previously. Cross-spectral BRS was calculated as mean value of the transfer function in the LF (BRS-LF) and HF band (BRS-HF).

Statistics
All data are expressed as mean±SEM. Interindividual differences were compared by the unpaired t test or the Mann–Whitney test. ANOVA testing for repeated measures was used for multiple comparisons. The data obtained during drug infusions were fitted to 4-parameter logistic functions (Boltzmann equation) for the complete data set and for men and women separately to obtain sigmoidal regression curves. The fitted baroreflex curves were compared according to Akaike’s information criteria to determine the model that was most likely to have generated the data (GraphPad Software). A value for P <0.05 was considered significant.

Results
Baseline blood pressure was similar in men and in women (Table 2). Heart rate tended to be higher in women. Heart rate variability in the time and in the frequency domain was reduced in women compared with men in our study population. However, the ratio between LF and HF heart rate oscillations was similar in both groups. MSNA, expressed as bursts per minute, bursts per 100 beats, and burst area per minute, was similar between women and men. MSNA was 21±3 bursts/min, heart rate was 66±3 bpm, blood pressure was 111±2/68±2 mm Hg in women who were taking birth control pills and 21±3 bursts/min, 64±2 bpm, and 109±3/63±2 mm Hg in women not taking birth control pills. Figure 1 illustrates the large variability in resting MSNA and the almost complete overlap between men and women. Furthermore, we did not observe significant correlations between MSNA and body mass index, waist circumference, hip circumference, or the waist-to-hip ratio.

Changes in systolic blood pressure with incremental infusion of phenylephrine and nitroprusside are illustrated in Figure 2. We did not find a gender difference in phenylephrine or nitroprusside responsiveness. Phenylephrine infusion at a rate of 0.8 µg/kg per minute increased systolic blood pressure 15±2.8 mm Hg in women and 14±2.1 in men (NS). Nitroprusside infusion at a rate of 0.8 µg/kg per min lowered systolic blood pressure 10±1.7 mm Hg in women and 9±1.1 mm Hg in men (NS).

To assess baroreflex regulation, we plotted R-R interval and MSNA against systolic blood pressure during phenylephrine and nitroprusside infusion (Figures 3 and 4). Baroreflex heart rate curves were similar in men and women, at least close to the operating point of the baroreflex. Individual pharmacological baroreflex gain was also similar in men and women (Figure 5, top; Table 2). The spontaneous baroreflex indices, calculated with the cross-spectral technique in the HF band and with the sequence technique, tended to be higher in men compared with women, but the difference did not reach significance (Table 2).

MSNA burst frequency increased as blood pressure was lowered with nitroprusside to a maximum of 48±4 bursts/min in men and 49±3 bursts/min in women (NS). MSNA burst incidence
increased to 58±4 bursts/100 beats in men and 58±5 bursts/100 beats in women (NS). The lowest MSNA burst frequency and burst incidence values during phenylephrine infusion were 5±1 bursts/min and 9±1 bursts/100 beats in men versus 7±2 bursts/min and 11±2 bursts/100 beats in women (NS). The gain of the baroreflex MSNA curves was similar in women and men (Figure 5, bottom; Table 2). The probability that 1 model fits the complete data set for men and women was 99.9% for baroreflex heart rate curves using a 4-parameter logistic function. However, the chances for congruence between men and women in terms of the MSNA baroreflex curves was 0.06% for burst rate, 0.4% for burst incidence, and 0.01% for burst area. Thus, at a given blood pressure, MSNA tended to be lower in women than in men.

**Discussion**

The main finding of our study was that baroreflex gains for heart rate and sympathetic MSNA regulation are similar in women and men. However, in women, the sympathetic baroreflex curve is shifted toward lower blood pressure values. Thus, at a given blood pressure, MSNA tends to be lower in women than in men. Our data provide further insight into the complex influences of gender on cardiovascular autonomic control.31

**Table 2. Resting Measurements (mean±SEM)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>59±1.2</td>
<td>65±2.5</td>
</tr>
<tr>
<td>R-R interval</td>
<td>1080±20</td>
<td>950±38</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114±2.1</td>
<td>110±2.6</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>65±1.5</td>
<td>66±1.9</td>
</tr>
<tr>
<td>MSNA frequency, bursts/min</td>
<td>19±2.8</td>
<td>21±2.5</td>
</tr>
<tr>
<td>MSNA incidence, bursts/100 beats</td>
<td>33±2.8</td>
<td>31±3.5</td>
</tr>
<tr>
<td>MSNA, burst area/min</td>
<td>0.75±0.15</td>
<td>0.70±0.13</td>
</tr>
</tbody>
</table>

Heart rate and blood pressure variability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSSD, ms</td>
<td>92±10</td>
<td>49±7</td>
</tr>
<tr>
<td>LF_RRI ms²</td>
<td>2500±570</td>
<td>760±230</td>
</tr>
<tr>
<td>HF_RRI ms²</td>
<td>1300±240</td>
<td>620±200</td>
</tr>
<tr>
<td>LF_RRI/HF_RRI</td>
<td>2.2±0.35</td>
<td>1.7±0.28</td>
</tr>
<tr>
<td>LF_SBP</td>
<td>11±2.1</td>
<td>5.0±0.92</td>
</tr>
</tbody>
</table>

BRS

Cross-spectral BRS-LF, ms/mm Hg | 19±2 | 14±2 |
Cross-spectral BRS-HF, ms/mm Hg | 37±3 | 26±6 |
Sequence technique BRS-up       | 28±3 | 21±3 |
Sequence technique BRS-down     | 25±2 | 21±3 |
Pharmacological BRS RRI, ms/mm Hg | 19±2 | 17±3 |
Pharmacological BRS MSNA, bursts/min per mm Hg | −1.9±0.2 | −2.0±0.3 |

RMSSD indicates square root of mean squared differences of successive R-R intervals; LF_RRI, R-R variability in LF range; HF_RRI, R-R variability in HF range; LF_RRI/HF_RRI, ratio between R-R variability in the LF and HF range; LF_SBP, systolic blood pressure variability in the LF range; cross-spectral BRS-LF, baroreflex heart rate sensitivity determined by cross-spectral analysis in the LF range; cross-spectral BRS-HF, baroreflex heart rate sensitivity determined by cross-spectral analysis in the HF range; BRS-up, baroreflex heart rate sensitivity determined by the sequence technique for increasing systolic blood pressure; BRS-down, baroreflex heart rate sensitivity determined by the sequence technique for decreasing systolic blood pressure; pharmacological BRS RRI and BRS MSNA, heart rate and sympathetic BRS determined with nitroprusside and phenylephrine infusion.

*P<0.05; †P<0.01.
Baroreflex blood pressure buffering is severely impaired. In a previous study, we compared responses to phenylephrine before and during near-complete ganglionic blockade to estimate baroreflex blood pressure function in women and men. Baroreflex blood pressure buffering was less effective in healthy young women compared with healthy young men. The phenomenon could be related to a gender difference in baroreflex heart rate or MSNA regulation.

In the present study, we applied phenylephrine and nitroprusside infusions to determine baroreflex heart rate and MSNA regulation. The slope of the baroreflex MSNA curves was virtually identical in men and women. However, the MSNA baroreflex curve was shifted toward lower blood pressure values. At a given blood pressure, MSNA tended to be lower in women than in men. Additional studies may be necessary to substantiate this observation. Baroreflex heart rate regulation determined with phenylephrine and nitroprusside infusion was similar in both groups. As shown in previous studies, baroreflex heart rate regulation tended to be decreased in women compared with men when we determined baroreflex heart rate regulation with spectral analysis or the sequence technique. Perhaps rapid spontaneous baroreflex-mediated heart rate changes and slower baroreflex-mediated heart rate changes during drug infusions are differentially influenced by gender.

In some but not all previous studies, MSNA was reduced in young women compared with young men. Resting
MSNA was similar in men and women in our study. Nevertheless, our study confirms the trend for a reduced MSNA in women. The sympathetic baroreflex curve was set to a lower blood pressure in women compared with men. Therefore, at a given blood pressure, MSNA was lower in women. For example, at a systolic blood pressure of 110 mm Hg, MSNA was \( \approx 25 \) bursts/min in women and 40 bursts/min in men (Figure 4, top). However, the gender difference in resting MSNA is much smaller than the range of MSNA measurements observed within each gender. Thus, gender is certainly not the crucial variable regulating resting MSNA.

Perspective

At first glance, our data are not consistent with a major difference in the ability of the baroreflex to regulate heart rate or sympathetic vasomotor tone in men and women. The observation might lead to the erroneous conclusion that baroreflex function in general is identical in women and men. However, in women, baroreflex regulation of sympathetic vasomotor tone is shifted to slightly lower blood pressures. In contrast, baroreflex heart rate curves appear to be set to a similar blood pressure in men and women. We speculate that the subtle shift in the sympathetic baroreflex curve in women changes the relative contribution of baroreflex output toward the heart and toward the vasculature. The issue is complicated by the fact that the shape of baroreflex curves is sigmoidal such that the steepness of the curves changes as blood pressure is manipulated. Thus, an important implication of our study is that baroreflex studies solely relying on determination of baroreflex gain may be misleading. The position of the baroreflex curves should also be considered. We will continue the research in this field to determine whether or not gender differences in baroreflex distribution contribute to the predisposition for women to experience postural tachycardia syndrome.43 The mechanisms contributing to the gender difference in baroreflex distribution are not known. Animal studies suggest that stimulation of estrogen receptors in central autonomic nuclei may play a role in this regard.44,45 Another possible explanation is a gender difference in norepinephrine transporter function.46 Norepinephrine transporter function strongly influences baroreflex distribution between tissues.9,10

Acknowledgments

The Deutsche Forschungsgemeinschaft and the Deutsches Zentrum fuer Luft und Raumfahrt supported the study.

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*Hypertension.* 2005;45:1159-1164; originally published online May 2, 2005; doi: 10.1161/01.HYP.0000165695.98915.9a

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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