Gender difference in cardiovagal baroreflex gain in humans

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Beske, Stacy D., Guy E. Alvarez, Tasha P. Ballard, and Kevin P. Davy. Gender difference in cardiovagal baroreflex gain in humans. J Appl Physiol 91: 2088–2092, 2001.—We tested the hypothesis that women would demonstrate lower cardiovagal baroreflex gain compared with men. If so, we further hypothesized that the lower cardiovagal baroreflex gain in women would be associated with their lower aerobic fitness and higher body fat percentage compared with men. To accomplish this, we measured cardiovagal baroreflex gain (modified Oxford technique) in sedentary, nonobese (body mass index < 25 kg/m²) men (age = 26.0 ± 2.1 yr, n = 11) and women (age = 26.9 ± 1.6 yr, n = 14). Resting R-R interval and diastolic blood pressure were similar in the two groups, but systolic blood pressure was lower (P < 0.05) in the women. Cardiovagal baroreflex gain was significantly lower in the women compared with the men (13.3 ± 1.5 vs. 20.0 ± 2.8 ms/mmHg, P < 0.05). The lower cardiovagal baroreflex gain in the women was not related (P > 0.05) to their lower aerobic fitness and was only marginally related to their higher body fat percentage (r = −0.34, P < 0.05). There were no gender differences in the threshold and saturation, operating range, or operating point (all P > 0.05), although the operating point fell significantly to left (i.e., at a lower systolic blood pressure) compared with men. Therefore, the findings of this study suggest that the gain of the cardiovagal baroreflex is reduced whereas other parameters were similar in women compared with men. The mechanisms responsible for the reduced cardiovagal baroreflex gain remain unclear.

vagal; baroreflex sensitivity; sex

ABRUPT DECREASES AND INCREASES in systolic arterial blood pressure produce baroreflex-mediated shortening and lengthening, respectively, of the R-R interval (13). This phenomenon, otherwise known as the cardiovagal baroreflex, is best described by the sigmoidal relation between R-R interval length and systolic blood pressure. The linear portion of this relation is used to derive the slope or gain of the cardiovagal baroreflex. Importantly, lower levels of cardiovagal baroreflex gain have been associated with poor orthostatic tolerance (5–7) and an increased risk of cardiovascular disease-related mortality (24, 25).

The influence of gender on cardiovagal baroreflex gain in humans is controversial: both similar (26, 34, 36) and lower (1, 4, 21, 23, 36) levels have been reported in women compared with men. There are a number of factors that could contribute to the disappointing findings in the past. For example, age (12, 19), hypertension (3, 19), oral contraceptive use (28), smoking (30), obesity (17), and physical activity/aerobic fitness (6–9, 22, 29) all have an important modulatory influence on cardiovagal baroreflex gain. Previous studies that addressed the influence of gender on cardiovagal baroreflex gain failed to control for these potentially confounding factors. Furthermore, the experimental approaches used to quantify cardiovagal baroreflex gain in previous studies likely differ in their ability to detect differences between men and women.

Accordingly, we tested the hypothesis that women would demonstrate lower cardiovagal baroreflex gain compared with men. Although women generally demonstrate lower aerobic fitness and higher body fat levels compared with men, there is no information available regarding whether these factors contribute to a gender difference in cardiovagal baroreflex gain. Therefore, we further hypothesized that the lower cardiovagal baroreflex gain in women, if observed, would be associated with their lower aerobic fitness and higher body fat level compared with men. To accomplish this, we measured cardiovagal baroreflex gain by using sequential intravenous bolus injections of sodium nitroprusside followed by phenylephrine HCl, i.e., the modified Oxford technique (11), in sedentary, nonobese men and premenopausal women. In contrast to other approaches, this approach produces robust linear gain estimates and full characterization of the sigmoidal relation between systolic blood pressure and R-R interval length. The latter allows the threshold, saturation, operating range, and operating point to be calculated. To date, no information is available regarding gender differences in these other cardiovagal baroreflex parameters. Importantly, to overcome limi...
tations of previous studies, we studied only nonsmoking sedentary, nonobese, and normotensive individuals 18–40 yr of age and women who were not taking oral contraceptives. Our findings indicate that cardiovagal baroreflex gain is lower in sedentary, nonobese premenopausal women compared with men. The lower cardiovagal baroreflex gain observed in women was not associated with their lower level of aerobic fitness and was only marginally related to their higher body fat percentage. There were no gender differences in the threshold and saturation, operating range, or operating point, although the operating point fell significantly to the left (i.e., at a lower systolic blood pressure) compared with men.

METHODS

Subjects. Eleven men and fourteen premenopausal women participated in the present study. All subjects were sedentary (no regular physical activity >20 min on more than 2 days/wk), nonobese (body mass index <25 kg/m²), and free from hypertension (<140/90 mmHg) or other overt cardiovascular diseases as assessed by casual blood pressure measurements and health history questionnaire, respectively. Subjects were further evaluated for the presence of overt cardiopulmonary disease by resting and maximal exercise electrocardiograms. All subjects were nonsmokers and were non-diabetic (2-h post glucose load <200 mg/dl), and none of the subjects were taking medications that could influence autonomic-circulatory function. None of the women were pregnant (confirmed by pregnancy test) or using oral contraceptives at the time of the study. All the women were eumenorrheic and were studied during the early follicular phase (days 3–5) of their menstrual cycle. The nature, purpose, risks, and benefits of the study were explained to each subject before informed consent was obtained. The Colorado State University Human Research Committee approved all experimental protocols.

Experimental procedures. Body mass was measured on a physician’s balance scale to the nearest 0.1 kg. Height was measured by using a stadiometer. Body composition was measured by using dual-energy X-ray absorptiometry (DPX-IQ, Lunar). Heart rate was measured from lead II of the electrocardiogram. Respiration was monitored by a pneumo-belt placed around the upper abdomen. Beat-to-beat arterial blood pressure was measured by using finger photoplethysmography (Finapres model 2300, Ohmeda). Resting Finapres arterial blood pressures were “calibrated” to brachial blood pressure during the experiment. Maximal oxygen consumption was measured during graded treadmill exercise to exhaustion. The fraction of expired oxygen and carbon dioxide and pulmonary ventilation were measured with the use of on-line computer-assisted open-circuit spirometry (TrueMax 2400, Parvomedics). The criteria for ensuring a valid maximal oxygen consumption has been described previously (14). The modified Oxford technique was used to quantify cardiovagal baroreflex gain (11).

Experimental protocol. All subjects were studied in the morning between 7:00 and 11:00 AM after a 12-h overnight fast. Subjects were instructed to refrain from caffeine and alcohol consumption for 24 h before all testing sessions. Subjects were also asked to avoid participation in vigorous physical activity for 24 h before testing.

An antecubital venous catheter was placed for the injection of vasoactive drugs. After at least 20 min of quiet rest and achievement of steady-state levels of heart rate, arterial blood pressure, and respiration, a bolus injection of sodium nitroprusside (75–100 µg) was given intravenously, followed 60 s later by a bolus injection of phenylephrine HCl (150 µg). In general, these pharmacological perturbations decreased and increased arterial blood pressure ~15 mmHg below and above baseline levels, respectively, during a 3-min period. During our pilot studies, we observed greater reductions in arterial blood pressure in women with a lower body mass index. Therefore, the 75-µg dose of sodium nitroprusside was used for six of the “smaller” women in the present study. Three trials were performed, and at least two acceptable trials were averaged for each individual (see Data Analysis below). Each trial was separated by at least 15 min.

Data analysis. Heart rate, arterial blood pressure, and respiration were recorded continuously and digitized at 500 Hz to a laboratory computer for later analysis using signal processing software (WinDaq, Dataq Instruments). A four-parametric sigmoid was fit to the data to calculate the cardiovagal baroreflex gain, saturation, threshold, operating point, and operating range (33) (see Fig. 1). The sigmoid relationship between systolic blood pressure and R-R intervals was determined. During our pilot studies, we observed greater reductions in arterial blood pressure in women with a lower body mass index. Therefore, the 75-µg dose of sodium nitroprusside was used for six of the “smaller” women in the present study. Three trials were performed, and at least two acceptable trials were averaged for each individual (see Data Analysis below). Each trial was separated by at least 15 min.
RESULTS

Subject characteristics. The characteristics of the subjects are shown in Table 1. There was no significant difference in age or body mass index. Body mass, height, and maximal oxygen consumption were lower in women compared with men, but body fat percentage was higher (all $P < 0.05$). Casually determined systolic blood pressure (104 ± 2 vs. 118 ± 3 mmHg) was significantly lower in women, but diastolic blood pressure (66 ± 3 vs. 60 ± 2 mmHg; $P > 0.05$) was not different. In addition, resting R-R interval (1,003 ± 41 vs. 1,012 ± 51 ms; $P > 0.05$) was similar in the two groups.

Cardiovagal baroreflex parameters. Cardiovagal baroreflex gain was ~35% lower ($P < 0.05$) in the women compared with men (Fig. 2). However, the threshold (691 ± 41 vs. 772 ± 29 ms), saturation (1,295 ± 53 vs. 1,217 ± 42 ms), and operating range (565 ± 50 vs. 468 ± 38 ms) were not significantly different in the women ($n = 12$) and men ($n = 11$). The operating point was also not different ($P > 0.05$), but fell significantly to the left in the women compared with men.

Correlations. Cardiovagal baroreflex gain was significantly correlated to body fat percentage ($r = -0.34$, $P < 0.05$) but not to any expression of maximal oxygen consumption ($P > 0.05$). The gender difference in cardiovagal baroreflex remained significant after adjusting for body fat percentage (13.3 ± 2.3 vs. 19.5 ± 2.8 ms/mmHg, $P < 0.05$).

DISCUSSION

There are several important findings of the present study. First, cardiovagal baroreflex gain was lower in women compared with men. Second, the lower cardiovagal baroreflex gain observed in women was not associated with their lower level of aerobic fitness. In addition, only a small portion of the variance (~10%) in cardiovagal baroreflex gain was accounted for by body fat percentage. Finally, the threshold, saturation, operating range, and operating point were similar, although the operating point fell at a significantly lower systolic blood pressure in the women compared with men.

Our findings are consistent with some (1, 4, 21, 23, 36) but not all (26, 34, 36) previous studies on this issue. The results of the present study extend previous findings in at least three important aspects. First, we controlled for a number of factors, including age, hypertension, oral contraceptive use, smoking, obesity, and physical activity, that potentially confounded the interpretation of previous studies on this issue.

Second, our findings were unique from previous studies in that the results of our study suggest that the lower cardiovagal baroreflex gain observed in women was not associated with their lower level of aerobic fitness and was only marginally related to their higher body fat percentage compared with men. Therefore, the results of the present study suggest that factors other than lower aerobic fitness and elevated body fat percentage must contribute to the lower cardiovagal baroreflex gain observed in women compared with men.

Finally, an important strength of our study was the use of sequential intravenous bolus injections of sodium nitroprusside followed by phenylephrine HCl to produce robust gain estimates and characterization of the entire sigmoid relationship between systolic blood pressure and R-R interval. In addition to quantifying cardiovagal baroreflex gain, the threshold and saturation regions, operating range, and operating point could also be derived. To our knowledge, our study is the first to use this experimental approach to investigate gender differences in cardiovagal baroreflex function.

The levels of cardiovagal baroreflex gain obtained in the present study are in the range of that reported in previous studies of healthy, young men and women that used similar approaches (i.e., bolus injection of vasoactive drugs) (1, 12). However, we would like to emphasize caution in comparing the values obtained in the present study with those obtained by others. This is particularly important when other experimental approaches to quantifying cardiovagal baroreflex gain are utilized because the gain estimate can vary considerably with the technique used and analysis performed. For example, the inclusion of threshold or saturation regions may produce smaller gain estimates than if they are excluded. Furthermore, the factors mentioned in the preceding paragraphs should also be considered

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men ($n = 11$)</th>
<th>Women ($n = 14$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>26.9 ± 16</td>
<td>26.0 ± 2.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161 ± 3</td>
<td>164 ± 2*</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>73.7 ± 2.3</td>
<td>59.5 ± 1.2*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23 ± 1</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>18.1 ± 1.6</td>
<td>29.7 ± 1.8*</td>
</tr>
<tr>
<td>V˙O₂max, ml·kg⁻¹·min⁻¹</td>
<td>48.0 ± 2.5</td>
<td>37.0 ± 1.6*</td>
</tr>
<tr>
<td>V˙O₂max, ml·kg FFM⁻¹·min⁻¹</td>
<td>61.1 ± 2.5</td>
<td>53.7 ± 3.1*</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; V˙O₂max, maximal oxygen consumption. *$P < 0.05$ vs. men.
when comparing our values for cardiovagal baroreflex gain with the values reported in the literature.

We can only speculate on the potential mechanisms responsible for the lower cardiovagal baroreflex gain in the women in the present study. First, it is possible that circulating estrogen and/or progesterone was responsible for the observed gender differences in the present study. However, 17β-estradiol administration enhances cardiovagal baroreflex gain in animals (31), and physiological fluctuations in estrogen and progesterone during the menstrual cycle do not appear to influence cardiovagal baroreflex gain in humans (27). Nonetheless, it is possible that female sex hormones exert an effect on cardiovagal baroreflex that is more chronic in nature.

Second, women have been reported to demonstrate lower carotid artery distensibility compared with men (20, 35). Carotid distensibility has been closely associated with cardiovagal baroreflex gain (2). Therefore, it is possible that lower levels of carotid artery distensibility in women would result in a smaller mechanical transduction of arterial blood pressure into baroreflexory stretch. This, in turn, would result in an attenuated cardiovagal baroreflex response. Future studies are necessary to address this issue.

There are some important implications of the present study that we would like to emphasize. First, women have been reported to demonstrate reduced orthostatic tolerance compared with men (4, 15, 16). There are a number of factors that have been attributed to the reduced orthostatic tolerance observed in women, including reduced cardiovagal baroreflex gain (4–6, 13). Therefore, our findings are consistent with the idea that a lower cardiovagal baroreflex gain in women may contribute to their reduced orthostatic tolerance compared with men. However, future studies will be needed to test this hypothesis directly.

Second, reduced cardiovagal baroreflex gain has been reported to be an important predictor of cardiovascular mortality (24, 25). Thus the lower cardiovagal baroreflex gain observed in the women in the present study would appear to present a paradox because premenopausal women demonstrate a reduced risk of cardiovascular disease (10). Presumably, more favorable levels of other risk factors (e.g., lipid and lipoprotein concentrations) in women would overwhelm any risk conferred by reduced cardiovagal baroreflex gain. However, as has been suggested previously (21), it is possible that the lower cardiovagal baroreflex gain in women could contribute to their poorer outcomes after myocardial infarction (18).

Finally, the results of our study suggest that gender should be considered separately in future studies focused on cardiovagal baroreflex function. However, an important issue not addressed in the present study is whether women respond differently to interventions directed at modifying cardiovagal baroreflex function.

There are some potential limitations of the present study that should be discussed. We studied only sedentary, nonobese men and women 18–40 years of age who were healthy and free of overt cardiovascular disease. As such, the influence of gender in other groups (e.g., older or obese adults) may differ from those reported here.

In summary, the results of the present study indicate that cardiovagal baroreflex gain is lower in women compared with men. The lower level of cardiovagal baroreflex gain was not associated with aerobic fitness and only marginally related to body fat content. In addition, the threshold, saturation, operating range, and operating point were similar, although the operating point fell significantly to the left (i.e., at a lower systolic blood pressure) in the women compared with men.

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