Gender differences in autonomic functions associated with blood pressure regulation

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Convertino, Victor A. Gender differences in autonomic functions associated with blood pressure regulation. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1909–R1920, 1998.—Functions of carotid and aortic baroreflex control of heart rate (HR), cardiopulmonary baroreflex control of vascular resistance, adrenoreceptor responsiveness, indexes of baseline vagal and sympathetic tone, circulating blood volume, and venous compliance were compared in men and women to test the hypothesis that lower orthostatic tolerance in women would be associated with lower responsiveness of specific mechanisms of blood pressure regulation. HR, stroke volume (SV), cardiac output (Q), mean arterial blood pressure (MAP), central venous pressure, forearm (FVR) and leg (LVR) vascular resistance, catecholamines, and changes in leg volume (%ΔLV) were measured during various protocols of lower body negative pressure (LBNP), carotid stimulation, and infusions of adrenoreceptor agonists in 7 females and 10 males matched for age and fitness. LBNP tolerance for the women (797 ± 63 mmHg/min) was 35% lower (P = 0.002) than 1,235 ± 101 mmHg/min for the men. At presyncope, SV, Q, MAP, and %ΔLV were lower (P < 0.05) in females compared with males, whereas HR, FVR, and total peripheral resistance were similar in both groups. Lower LBNP tolerance in females was associated with reduced HR response to carotid baroreceptor stimulation, lower baseline cardiac vagal activity, greater decline in Q induced by LBNP, increased β₁-adrenoreceptor responsiveness, greater vasoconstriction under equal LBNP, lower levels of circulating NE at presyncope, and lower relative blood volume. The results of this investigation support the hypothesis that women have less responsiveness in mechanisms that underlie blood pressure regulation under orthostatic challenge.

baroreflex; orthostasis; orthostatic hypotension; vasoconstriction

LOW RESPONSIVENESS of cardiovascular mechanisms that normally contribute to regulation of blood pressure and maintenance of cerebral perfusion could increase the risk of failure for task performance by enhancing the potential for loss of consciousness. Recent data reported from several investigations provide evidence that females have lower tolerance to various orthostatic challenges compared with males. In one study (23), tolerance to lower body negative pressure (LBNP) was 15% lower in women than men. In another study (30), six men and four women were exposed to three tests consisting of 20, 40, and 60 mmHg LBNP for 5 min each. Although this experiment was not designed to determine orthostatic tolerance, it was reported that all men completed all LBNP tests, whereas women completed only 2 of 12 tests. Women have demonstrated greater incidence of syncopal episodes during standing after spaceflight (17) and lower predicted tolerance to passive +3 G, acceleration (28). In more recent experiments designed to elicit tolerance, orthostatic performance was 22–61% lower in women than men (22, 37).

Orthostatic compromise may include increased venous compliance of the lower extremities (21, 29), reduced blood volume (1, 3, 27), impaired baroreflex function (3–5, 10, 13), and decreased cardiac filling pressure and left ventricular end-diastolic volume, with consequent lowering of stroke volume and cardiac output (Q) (25). It is reasonable to suspect that differences in orthostatic tolerance between men and women are associated with differences in some or all of these mechanisms. When measured at the same absolute orthostatic challenge (e.g., 50 mmHg LBNP), women demonstrate greater heart rate (HR) (16, 24, 30), less increase in systemic vascular resistance (15), and less blood pooling in the legs (15), with greater blood pooling in the pelvic region (38). These observations seem to indicate that women have less-responsive cardiovascular functions compared with those of men and have led to the hypothesis that women may respond to orthostatic challenges with vagal withdrawal, whereas men may respond with greater sympathetic stimulation to the peripheral vasculature (15, 16). However, previous investigations have not elucidated differences between men and women in various cardiovascular characteristics and autonomic functions that are associated with differences in orthostatic responses. Therefore, functions of carotid and aortic baroreflex control of HR, cardiopulmonary baroreflex control of vascular resistance, adrenoreceptor responsiveness, neuroendocrine responsiveness, indexes of baseline vagal and sympathetic tone, circulating blood volume, and venous compliance were measured and compared in men and women to test the hypothesis that greater orthostatic intolerance in women would be associated with lesser responsiveness of specific mechanisms that underlie blood pressure regulation.

METHODS

Subjects. Seven women and ten men matched for age volunteered to participate as subjects for this investigation after all procedures and risks associated with the experiments were explained, and their voluntary written informed consent to participate in the study was obtained as required by AFI 40–402. All procedures were approved by the Institutional Review Board at Brooks Air Force Base, TX. The physical characteristics of the groups are presented in Table 1. All subjects were nonsmokers and normotensive, and their selection into the study was based on results of a screening evaluation comprised of a detailed medical history, physical

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HR,

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V\(\dot{O}_2\)max. The exercise protocol began with the subject walking and 3 days of tests and measurements of physical and procedures.

prescription drugs, 48 h before testing. During an orienta-

tion and treadmill electrocardiogram to assure absence of hyperthyroidism or taking prescription drugs were excluded, participation to assure that they were not pregnant during the experiments. No female subjects were using oral contraceptives. Because of potential effects on vascular volume and baroreflex functions, subjects were asked to refrain from exercise and stimulants, such as caffeine and other non-prescription drugs, 48 h before testing. During an orientation period that preceded the experiments, subjects were made familiar with the laboratory, the protocol, and procedures.

Experimental protocol. The experimental protocol consisted of 3 days of tests and measurements of physical and physiological functions. On day 1, subjects underwent the following tests: 1) cardiopulmonary baroreflex control of peripheral vascular resistance, 2) aortic baroreflex control of HR, 3) adrenergic receptor responsiveness, and 4) measurement of blood volume. On day 2, subjects underwent measurements for 1) HR variability, 2) carotid baroreflex control of HR, 3) HR and blood pressure responses to a Valsalva maneuver, 4) measurement of leg volume and compliance, and 5) tolerance to LBNP. On day 3, subjects underwent tests for measurement of their maximal oxygen uptake (\(V_{O2max}\)) and estimated body composition. All tests conducted on days 1 and 2 were always separated from \(V_{O2max}\) tests by a minimum of 24 h. All measurements were conducted at the same time of day and in the same sequence.

\(V_{O2max}\). A graded treadmill protocol was used to elicit \(V_{O2max}\). The exercise protocol began with the subject walking at a speed of 2.0 miles per hour (mph) and 0% grade for 1 min followed by 3.0 mph for 2 min. At constant grade (0%), the treadmill speed was increased by 1 mph each 30 s until the subject indicated that he/she had reached a comfortable running speed. At this point in the test, speed was main-

tained constant and the grade of the treadmill was increased by 2% every minute until the subject reached volitional exhaustion. Subjects breathed through a low-resistance valve, and the volume and composition of expired gas was collected and analyzed on a Beckman model H metabolic measurement cart for the fractions of mixed expired oxygen and carbon dioxide. Because body fat contributes significantly to the calculated difference in \(V_{O2max}\) between males and females (12), \(V_{O2max}\) was expressed as a function of estimated lean body mass (ml·kg·LBM⁻¹·min⁻¹) for the purpose of matching the fitness levels of our men and women (11).

Estimation of body composition. Skinfolds were taken at five sites for the females (thigh, ilium, abdomen, triceps, and six sites for the males (chest, thigh, ilium, abdomen, triceps, and scalpula). The sum of the skinfold measurements for each gender was used to estimate percentage of body fat according to the formula of Pollock et al. (31).

LBNP. Orthostatic tolerance was determined while the subject was in the supine posture by progressively reducing pressure around the lower body relative to ambient pressure. The LBNP protocol consisted of a 2-min baseline period followed by decompression to \(-15\) and \(-30\) mmHg for 10 min each. Further 10-mmHg reductions in pressure were added every 3 min until test termination. The duration of the test was determined by 1) completion of 3 min at \(-100\) mmHg, 2) onset of presyncopal symptoms including a drop in systolic blood pressure \(\geq 15\) mmHg and or sudden bradycardia \(\geq 15\) beats, 3) progressive reduction in systolic blood pressure to \(<80\) mmHg, and 4) onset of symptoms such as nausea, sweating, gray-out, or dizziness. In the present experiment, all female and male subjects expressed one or more subjective symptoms that coincided with a reduction in systolic blood pressure to \(\leq 80\) mmHg. A cumulative stress index for LBNP tolerance was derived by summing the products of negative pressure in millimeters of mercury and time in minutes during each pressure stage (29).

Hemodynamic measurements. Baseline systolic and diastolic arterial blood pressures were measured noninvasively from the left arm with a Collins automated sphygmomanometer blood pressure measurement device. In addition, beat-by-beat continuous measurement of arterial blood pressure was monitored during Valsalva maneuvers, tests for adrenoreceptor responsiveness, and LBNP exposures using finger photoplethysmographic techniques (Finapres, Ohmeda) with the hand held at the level of the midsuternum. Total finger arterial blood pressure, the blood pressure finger cuff was maintained constant by modulating cuff pressure in parallel with intraarterial pressure with the use of an electropneumatic servo-feedback system and measured with an infrared photoplethysmograph. Blood pressure measurements obtained by auscultation were used to verify readings obtained from the Finapres. Mean arterial pressure (MAP) was calculated by dividing the sum of systolic pressure and twice diastolic pressure by three. Four silver tape electrodes, two around the neck and two around the thorax, were attached to a Minnesota Impedance Cardiograph (model 304B) for noninvasive rheographic determination of stroke volume during rest and LBNP (6). Briefly, stroke volume was calculated as the product of the resistivity of blood (calculated from hematocrit), the average distance between the inside electrode bands, the baseline impedance of the thorax, the ejection time (measured horizontally on the impedance cardiogram from the start of steep upstroke to downward deflection at the end of ejection), and the amplitude from the baseline to peak of the impedance cardiogram tracing. Continuous HR was recorded during all tests using a four-lead electrocardiogram. Q during rest and LBNP was calculated as the product of HR and stroke volume. Total systemic peripheral resistance (TPR) was calculated by dividing MAP by Q. Changes in leg volume during each LBNP stage were measured with a strain gauge placed around the point of maximum girth of the left calf. Percentage changes in

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<th>Table 1. Subject descriptive data</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Age, yr</td>
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<td>Height, cm</td>
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<td>Weight, kg</td>
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<td>Estimated body fat, %</td>
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<td>Rest SBP, mmHg</td>
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<td>Rest DBP, mmHg</td>
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<td>Rest heart rate, beats/min</td>
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<td>Max heart rate, beats/min</td>
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<td>(V_{O2max},) ml·kg⁻¹·min⁻¹</td>
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<td>(V_{O2max},) ml·kg⁻¹·min⁻¹</td>
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Values are means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; \(V_{O2max}\), maximal oxygen uptake; LBM, lean body mass.
calf volume (ml/100 ml) were calculated from circumference changes.

Forearm and leg blood flows were measured by venous occlusion plethysmography with the use of a dual loop mercury-in-Silastic strain gauge placed around the left forearm or calf at the point of maximal circumference. Venous outflow from the forearm or calf was prevented by the placement of a cuff around the brachium just above the elbow or around the thigh just above the knee using an occlusion pressure of −40 mmHg for the arm and −60 mmHg for the leg. Arterial occlusion to reduce blood flow to the hand or foot was applied by a wrist or an ankle cuff inflated at a pressure of −250 mmHg. After wrist or ankle cuff inflation for 1 min, venous occlusion was initiated for 10 s followed by its release for 10 s for six sequential occlusions. The relative change (percent) in strain gauge length over 10 s was quantified as a volume of blood per unit time, i.e., flow. Ten-second occlusions were repeated during the final 2 min of drug infusion at each stage of the adrenoreceptor tests (leg) and LBNP tests (forearm), and the average of the six measurements represented the flow for that test condition. An index of forearm or leg vascular resistance was calculated by dividing MAP by expressed as peripheral resistance units (PRU in average flow during the final 2 min of each test condition and leg vascular resistance was calculated by dividing MAP by presented the flow for that test condition. An index of forearm or leg vascular resistance was calculated by dividing MAP by average flow during the final 2 min of each test condition and expressed as peripheral resistance units (PRU in mmHg·min·100 ml·ml−1)

Subjects lay in the right lateral decubitus position, and a 20-gauge catheter was inserted into an antecubital vein of the dependent right arm for measurement of estimated central venous pressure (CVP). Under these conditions, the pressure in the large vein of the right arm reflects CVP when the pressure transducer is centered at heart level (18). The catheter was then cleared with isotonic saline solution and connected to a Baxter Uniflow model 43–260 pressure transducer for measurement of venous pressure. Before connection to the catheter, the transducer was positioned at the level of the midsternum with a ruler and level and was calibrated with a known 20-mmHg pressure introduced from a digital manometer (Omega).

Leg volume and compliance. A series of five circumference measurements placed 5 cm apart on each thigh and calf was performed on each subject. The total geometric volume of each thigh and calf segment was estimated by calculating the volume of each sequential segment from its midcircumference value and length and summing the values of all segments. This procedure assumes that each segment approximates the shape of a cylinder. Total leg volume was calculated as the sum of all segments of both legs. Compliance of both legs was measured during supine rest using a Whitney strain gauge placed at the point of greatest calf circumference. After 30 min of supine control, the left leg was slightly elevated (~4 in) at the ankle and an occlusion cuff placed just above the knee was inflated to 30 mmHg for 180 s. Leg compliance was calculated by dividing the volume change (ml/100 ml) at a plateau (i.e., point at which venous pressure equals cuff pressure) by the cuff pressure and expressed as $\Delta V/\Delta P$. mmHg. The value for leg compliance was multiplied by 100 for convenience.

HR variability. Each subject underwent collection of electrocardiogram data during 5 min in which the respiratory rate was controlled by the subject breathing at a constant rate of 15 breaths/min with the use of a metronome. An index of cardiac vagal activity was assessed by calculating the standard deviation of R-R intervals.

Measurement of carotid-cardiac baroreflex. A Silastic neck chamber device covering the area of the carotid arteries was used to elicit carotid baroreceptor stimulus-cardiac reflex response relationships. The stimulus profile produced a series of stair-stepped neck pressure reductions from −40 to −65 mmHg that were superimposed on seven successive carotid arterial pulses (5). Systolic pressure was measured via auscultation before and after each neck chamber test session, and carotid pressure was calculated as systolic pressure minus neck chamber pressure applied during the heat beat. A stimulus-response relationship of the baroreflex was derived by plotting R-R intervals at each pressure step against respective carotid distending pressure. From the average of each five-trial sequence of responses, baroreflex relationships were reduced to the following parameters for statistical comparisons: 1) maximum slope to provide an index of reflex sensitivity, 2) position of operational point [control R-R − minimum R-R]/range × 100% to provide information about the position from which the baseline HR functions on the stimulus-response relationship, and 3) the estimated carotid pressure at maximum slope, i.e., point halfway between the pressures bracketing the maximum slope, to identify the point of maximal buffering. To determine the segment with the steepest slope, least-squares linear regression analysis was applied to every set of three consecutive points on the response relationship.

Measurement of aortic-cardiac baroreflex. Subjects were instrumented for beat-to-beat measurements of HR, arterial pressures, and estimated CVP and were placed in the LBNP chamber. After instrumentation, subjects rested quietly for 15 min, after which 3 min of baseline data were obtained. The aortic-cardiac baroreflex was assessed using a technique previously described (34). The protocol was initiated with a steady-state infusion of phenylephrine (PE) into an antecubital vein of the arm opposite to that used for estimating CVP, with a goal of increasing MAP by 15 mmHg. LBNP was applied (ranging from 5 to 20 mmHg) until estimated CVP was returned to pre-PE infusion levels, and neck pressure equal to 1.4 times the increase in MAP (26) was then applied to the anterior two-thirds of the neck with the intention of returning mean carotid sinus transmural pressure to pre-PE infusion values. Clamping of CVP and carotid pressure at baseline levels by application of LBNP and neck pressure, respectively, was designed to remove PE-induced loading of cardiopulmonary and carotid baroreceptors, thereby isolating the influence of the aortic baroreceptors. Responsiveness of the aortic baroreflex control of HR was calculated as the ratio of the difference in HR to MAP (ΔHR/ΔMAP) between pre-PE infusion and post-PE infusion with LBNP and neck pressure.

Measurement of cardiopulmonary baroreflex control of FVR. After a 2-min baseline rest period with LBNP pressure at 0 mmHg, subjects underwent continuous decompression at 5, 10, 15, and 20 mmHg every 2 min. The LBNP protocol was designed to selectively elicit the vascular constriction response caused by unloading the cardiopulmonary baroreceptors, because arterial blood pressures are not altered (6). Forearm blood flow and CVP were measured continuously throughout the LBNP test. A stimulus-response relationship of the baroreflex was derived by plotting CVP against respective FVR, and the responsiveness of the reflex was determined by calculating the slope from least-squares linear regression analysis.

Measurement of baroreflex responses to Valsalva maneuver. Each subject underwent a Valsalva maneuver that consisted of 15 s normal breathing to establish baseline, 15 s of Valsalva strain at 30 mmHg expiratory pressure, and 30 s poststrain (9). HR and blood pressure responses from three trials were averaged in a phase-by-phase manner for baseline, phase I, early phase II, and late phase II. For phase I, ΔMAP was used in the analyses as an index of the effects of vascular volume (35). For late phase II, ΔMAP was used in the analyses as a...
marker for sensitivity of baroreflex-mediated control of peripheral vascular resistance (33). The ratio ΔHR to ΔMAP was used in the analyses for early phase II because of its usefulness in describing integrated cardiac baroreflex responsiveness (33, 35).

Measurements of adrenergic receptor responsiveness. After baseline measurements of HR, blood pressure, and leg blood flow, three graded infusions of α- and β-adrenergic agonists were performed with isotonic saline as a vehicle. Each infusion interval was 9 min in duration to establish steady state and allow adequate time for all measurements. The protocol and doses of adrenergic agonists were determined by laboratory experience to produce safe but significant physiological responses (8). The total volume infused was <50 ml. A recovery period of at least 25 min was allowed between the two agonist infusion protocols to allow hemodynamic measurements to return to preinfusion baseline levels. During both infusion protocols, constant monitoring of beat-to-beat blood pressure and HR was performed and leg blood flows were measured at each infusion level.

α1-Adrenergic receptor responsiveness. Graded infusion of the α1-adrenergic agonist PE was used to assess the responsiveness of these vascular receptors. PE was infused at three graded constant rates of 0.25, 0.50, and 1.00 μg·kg⁻¹·min⁻¹. An elevation of systolic blood pressure of 20 mmHg above or reflex reduction of HR 20 beats/min below resting baseline was a predetermined end point for test termination. No tests were terminated using these criteria. The response of α1-adrenergic receptors was assessed by relating the PE dose with the reduction in leg vascular resistance. The relationships between PE doses and leg vascular resistance were linear, and the slopes describing these relationships were used to represent an index of α1-adrenergic receptor responsiveness.

β1-Adrenergic receptor responsiveness. After HR and blood pressure had been allowed to return to baseline levels after PE infusions, infusions of isoproterenol (Iso) were used to assess the responsiveness of β1- and β2-adrenergic receptors. Iso was infused at three graded constant rates of 0.005, 0.01, and 0.02 μg·kg⁻¹·min⁻¹. An elevation of HR by 35 beats/min above resting baseline was the predetermined end point for test termination. The test for one of the female subjects was terminated during the final infusion rate using this criteria. Linear regression relationships were then constructed relating the increase in HR and the decrease in leg vascular resistance to the dose of Iso. The slopes describing the linear stimulus-response relationship between the dose of Iso and HR and leg vascular resistance provided a measure of the systemic responsiveness of β1- and β2-adrenergic receptors, respectively.

Plasma measurements. A 30-ml antecubital venous blood sample was taken without stasis before and immediately after termination of the LBNP test to determine the response of norepinephrine (NE), epinephrine (Epi), arginine vasopressin (AVP), and plasma renin activity (PRA) to orthostasis. Immediately after each withdrawal, whole blood was taken from the syringe and transferred to a chilled tube containing sodium EDTA. Microhematocrit and hemoglobin (Coulter S-4 system) were measured in triplicate using a 1 ml of the EDTA-treated whole blood. The remaining whole blood was centrifuged at 2,000 g for 20 min at 4°C. Immediately after centrifugation, the plasma was aliquoted for NE, Epi, AVP, and PRA and stored frozen until hormonal assays were performed. Radioimmunoassay procedures were used to analyze plasma AVP (Instar Nuclear), and PRA (Biotec RIA kit) and plasma NE and Epi concentrations were measured by high-performance liquid chromatography (Waters) according to standardized procedures (7). Plasma volume was determined by a modified dilution technique (7, 20) using sterile solutions of Evans blue dye (The New World Trading Corporation). Total blood volume was calculated from the plasma volume and peripheral venous hematocrit measurements. These procedures produced high test-retest correlation coefficients in our laboratory (7, 20). Total circulating plasma NE and Epi were calculated as the product of plasma volume and plasma NE and Epi concentrations as an index of baseline sympathetic activity and catecholamine release during LBNP (19).

Statistical analysis. Descriptive statistics were performed for all variables. Results are presented as means ± SE. A one-way analysis of variance was performed for comparisons between the two groups of all variables and slopes of responses. A multivariate analysis of variance was used for group comparisons across LBNP levels.

RESULTS

Subjects. A summary of the descriptive data for the subjects in the two gender groups, together with the resultant F and P values from statistical analyses, is presented in Table 1. The female group had lower (P < 0.027) height, weight, baseline systolic blood pressure, and VO2max expressed per body weight and higher (P < 0.009) baseline HR and estimated body fat. Age, maximal HR, and VO2max expressed per kilogram of LBM were not statistically distinguishable between the two groups.

Responses to LBNP. All subjects demonstrated intolerance to LBNP by the onset of presyncope symptoms, including a drop in mean blood pressure <80 mmHg with subsequent bradycardia and various degrees of symptoms such as nausea, sweating, or dizziness. Cumulative LBNP index for the women (819 ± 85 mmHg/min) was 35% lower [F(1,15) = 8.73; P = 0.010] than 1,235 ± 101 mmHg/min for the men (Fig. 1). At the LBNP level at which presyncope occurred, there were no distinguishable differences between females and males in HR, TPR, and FVR. However, females demonstrated lower (P ≤ 0.050) stroke volume, Q, MAP, and leg pooling than the males at the point of

![Fig. 1. Individual and average cumulative index for lower body negative pressure (LBNP) tolerance in females and males.](http://ajpregu.physiology.org/Downloadedfrom)
The females had greater elevations in thoracic impedance during LBNP at the point of presyncope (2.1 ± 0.3 Ω) compared with the males (0.7 ± 0.2 Ω).

HR, stroke volume, Q, MAP, TPR, and FVR responses to graded LBNP from 0 to –50 mmHg are illustrated in Fig. 2. Both females and males demonstrated gradual reduction in stroke volume with a subsequent decrease in Q despite a compensatory elevation in HR. MAP showed little change in the face of lower Q as a result of increased peripheral vascular resistance. The rate, i.e., slope, of elevation in HR and TPR and FVR and reduction in Q were greater in the females than in the males (Table 3). Percentage increase in leg volume during graded LBNP from 0 to –50 mmHg was greater in females than in males.
Table 3. Hemodynamic responses (slopes) to graded LBNP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n = 10)</th>
<th>Women (n = 7)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate slope, beats·min⁻¹·mmHg⁻¹</td>
<td>0.37 ± 0.05</td>
<td>0.58 ± 0.10</td>
<td>4.236</td>
<td>0.057</td>
</tr>
<tr>
<td>Stroke volume slope, ml/mmHg</td>
<td>−1.06 ± 0.10</td>
<td>−1.23 ± 0.19</td>
<td>0.664</td>
<td>0.428</td>
</tr>
<tr>
<td>Cardiac output slope, l·min⁻¹·mmHg⁻¹</td>
<td>−0.03 ± 0.01</td>
<td>−0.07 ± 0.01</td>
<td>12.757</td>
<td>0.003</td>
</tr>
<tr>
<td>MAP slope, mmHg/mmHg</td>
<td>−0.15 ± 0.03</td>
<td>−0.16 ± 0.04</td>
<td>0.053</td>
<td>0.821</td>
</tr>
<tr>
<td>FVR slope, PRU/mmHg</td>
<td>0.18 ± 0.10</td>
<td>0.45 ± 0.06</td>
<td>4.251</td>
<td>0.057</td>
</tr>
<tr>
<td>TPR slope, PRU/mmHg</td>
<td>0.07 ± 0.02</td>
<td>0.25 ± 0.03</td>
<td>23.485</td>
<td>0.0002</td>
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</table>

Values are means ± SE.

[F(1,13) = 9.482, P = 0.009] in males compared with females, whereas the elevation in thoracic impedance was less [F(1,14) = 85.033, P < 0.0001] in males (Fig. 3).

HR variability. The average standard deviation of R-R intervals during controlled breathing was less [F(1,15) = 4.919, P = 0.042] in women (39.5 ± 3.9 ms) compared with an average response of 64.2 ± 8.8 ms in the men.

Baroreflex responses. Average stimulus-response relationships of the carotid baroreflex control of heart rate (R-R interval) for women and men are plotted in Fig. 4. Females and males demonstrated similar operational points [35.7 ± 9.3 and 38.9 ± 7.8%, respectively; F(1,15) = 0.066, P = 0.801] and carotid distending pressures at maximum slope [126 ± 12 and 124 ± 6 mmHg, respectively; F(1,15) = 0.039, P = 0.855] for the carotid baroreflex relationship. However, carotid-cardiac baroreflex responsiveness, i.e., maximum slope of the stimulus-response relationship, was lower [F(1,15) = 4.679, P = 0.047] in the women (2.61 ± 0.41 ms/mmHg) compared with that in the men (3.93 ± 0.41 ms/mmHg). Aortic-cardiac baroreflex sensitivity in the women (−1.05 ± 0.57 beats·min⁻¹·mmHg⁻¹) could not be statistically distinguished [F(1,15) = 0.407, P = 0.533] from that in the men (−0.71 ± 0.20 beats·min⁻¹·mmHg⁻¹).

Average stimulus-response relationships of the carotid-pulmonary baroreflex control of FVR for women and men are plotted in Fig. 5. Differences in slopes (ΔFVR/ΔCVP) between the gender groups were compared by analyzing the least-squares linear estimates generated by each subject. Average ΔFVR/ΔCVP of the carotid-pulmonary baroreflex response was −4.6 ± 1.8 PRU/mmHg in the women compared with −2.6 ± 0.3 PRU/mmHg in the men [F(1,15) = 1.710, P = 0.200].

Women demonstrated similar [F(1,15) = 0.235, P = 0.635] elevation in MAP (ΔMAP = 20.9 ± 2.4 mmHg) during phase I of the Valsalva maneuver compared with that of the men (ΔMAP = 19.5 ± 1.8 mmHg). The rise in MAP during late phase II observed in the women (ΔMAP = 18.3 ± 5.3 mmHg) compared with the men (ΔMAP = 10.8 ± 1.7 mmHg) could not be distinguished statistically [F(1,15) = 2.423, P = 0.140]. However, the ΔHR/ΔMAP during early phase II was greater [F(1,15) = 6.796, P = 0.020] in the men (−1.3 ± 0.2 beats·min⁻¹·mmHg⁻¹) than in the women (−0.7 ± 0.2 beats·min⁻¹·mmHg⁻¹) as a result of a greater tachycardic response in the males with the same hypotensive stimulus.

Adrenergic receptor responsiveness. The average slope of the individual subject dose-response relationships be-
between Iso and HR was greater \[ F(1,15) = 9.864, P = 0.007 \] in the females (2,053 ± 170 beats·µg\(^{-1}·kg\(^{-1}·min\)) compared with an average response of 1,323 ± 153 beats·µg\(^{-1}·kg\(^{-1}·min\)) in the males. Figure 6, top, represents the regressions calculated from the mean (±SE) HRs at each Iso level. The average slope of the arterial blood pressure response to Iso was not distinguishable \[ F(1,15) = 0.082, P = 0.779 \] between females (224 ± 113 mmHg·µg\(^{-1}·kg\(^{-1}·min\)) and males (298 ± 142 mmHg·µg\(^{-1}·kg\(^{-1}·min\)). In contrast, there were no statistical differences between females and males in the average slope of the individual subject dose-response relationships between Iso and leg vascular resistance \[ 2,629 ± 248 and 2,690 ± 294 PRU·µg\(^{-1}·kg\(^{-1}·min\), respectively; F(1,15) = 0.022, P = 0.883 \] or between PE and leg vascular resistance \[ 16.7 ± 5.1 and 19.5 ± 4.7 PRU·µg\(^{-1}·kg\(^{-1}·min\), respectively; F(1,15) = 0.157, P = 0.698 \]. The regressions calculated from the mean (±SE) leg vascular resistances at each Iso and PE level are presented in Fig. 6, bottom.

Leg volume and compliance. Total leg volumes of the women (11.8 ± 0.7 liters) and men (12.0 ± 0.5 liters) were similar \[ F(1,15) = 0.058, P = 0.813 \], whereas calf compliance of the men (6.2 ± 0.5 ml/mmHg) could not

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**Fig. 5.** Cardiopulmonary baroreflex stimulus-response relationship between forearm vascular resistance and estimated central venous pressure in females ( ●, solid lines) and males ( ○, dashed lines). Linear equation for the mean female response is \( y = -3.62x - 70.7 \) \( (r^2 = 0.978) \) and for the mean male response is \( y = -2.46x - 57.8 \) \( (r^2 = 0.933) \). Symbols are means ± SE.

**Fig. 6.** Dose-response relationships between isoproterenol (Iso) and heart rate (top), between Iso and leg vascular resistance (middle), and between phenylephrine (PE) and leg vascular resistance (bottom) for females ( ●) and males ( ○). Linear regressions are calculated from mean values. For Iso vs. heart rate, the linear equation for females is \( y = 1.880x - 61.8 \) \( (r^2 = 0.995) \) and for males is \( y = 1.303x - 52.6 \) \( (r^2 = 0.993) \). For Iso vs. leg vascular resistance, the linear equation for females is \( y = -865x - 48.5 \) \( (r^2 = 0.957) \) and for males is \( y = -690x - 51.7 \) \( (r^2 = 0.876) \). For PE vs. leg vascular resistance, the linear equation for females is \( y = 16.0x - 47.6 \) \( (r^2 = 0.903) \) and for males is \( y = 19.5x - 45.4 \) \( (r^2 = 0.948) \). †Slopes of responses with \( P = 0.007 \).
be distinguished statistically \( F(1,15) = 1.908, P = 0.187 \) from that of the women \((5.0 \pm 0.7 \text{ ml/mmHg})\).

Plasma volume and endocrine responses. When vascular volumes were standardized for body weight, the average blood volume of females \((59.3 \pm 4.6 \text{ ml/kg})\) was less \( F(1,13) = 5.530, P = 0.035 \) compared with males \((71.5 \pm 3.8 \text{ ml/kg})\), primarily as a result of lower \( F(1,13) = 4.230, P = 0.060 \) circulating red blood cell volume \((23.9 \pm 2.7 \text{ for females vs. } 31.0 \pm 1.7 \text{ ml/kg for males})\). Average plasma volume was \(38.7 \pm 3.3 \text{ in females and } 40.5 \pm 2.3 \text{ ml/kg in males} \[ F(1,13) = 0.206, P = 0.658 \].

Baseline plasma NE, Epi, and PRA were similar between the gender groups, whereas females displayed twice the level of baseline plasma AVP as males (Fig. 7). Presyncopal LBNP induced an elevation \([ F(1,10) = 41.524, P < 0.0001 \]) of total circulating NE to \(1,770 \pm 315 \text{ in females and } 2,214 \pm 306 \text{ ng in males} \) (Fig. 7). The change in total circulating plasma NE from baseline to presyncopal LBNP in the females \((694 \pm 95 \text{ ng})\) was less \([ F(1,10) = 5.015, P = 0.049 \]) than the elevation of \(1,345 \pm 275 \text{ ng observed in the males, Presyncopal LBNP induced an elevation} [ F(1,10) = 6.458, P = 0.029 ] \) of total circulating Epi to \(383 \pm 164 \text{ ng in females and } 262 \pm 90 \text{ ng in males} \) (Fig. 7). The change in total circulating plasma Epi from baseline to presyncopal LBNP in the females \((232 \pm 150 \text{ ng})\) was not statistically discernible \([ F(1,10) = 0.912, P = 0.360 \]; Fig. 7\).

DISCUSSION

The results of the present study confirm those of previous investigations \((17, 22, 23, 28, 30, 37)\) that women have significantly lower capacity to regulate blood pressure and maintain orthostatic function compared with men. Because greater height predicts lower LBNP tolerance \((27)\), shorter females might be expected to have an advantage in tolerance over taller males. Lower LBNP tolerance in females in light of their height advantage underscores important differences between genders in underlying cardiovascular mechanisms. This investigation expanded on previous work by identifying specific characteristics of cardiovascular functions that supported the hypothesis that greater orthostatic intolerance in women was associated with less responsiveness of specific mechanisms of blood pressure regulation. The unique finding of this study was that presyncopal predisposition in females was associated with less HR response to carotid baroreceptor stimulation, lower baseline cardiac vagal activity and systolic blood pressure, greater decline in \(Q\) induced by LBNP, increased \(\beta_1\)-adrenoreceptor responsiveness, greater vasoconstriction under equal LBNP, lower levels of total circulating NE at presyncope, and lower blood volume.

Some investigations have suggested that orthostatic tolerance may be reduced in athletically trained indi-

![Fig. 7. Response of plasma norepinephrine (NE), epinephrine, arginine vasopressin, and plasma renin activity to presyncope LBNP in female (•, solid lines) and male (○, dashed lines) subjects. *P < 0.05 from baseline to syncope; †P < 0.05 between females and males for change in NE from baseline. Symbols are means ± SE.](http://ajpregu.physiology.org/)

Fig. 7. Response of plasma norepinephrine (NE), epinephrine, arginine vasopressin, and plasma renin activity to presyncope LBNP in female (•, solid lines) and male (○, dashed lines) subjects. *P < 0.05 from baseline to syncope; †P < 0.05 between females and males for change in NE from baseline. Symbols are means ± SE.
individuals with high \( V_{O_{2\text{max}}} \) (1). To minimize this confounding factor, the criteria of expressing \( V_{O_{2\text{max}}} \) as the rate of systemic oxygen uptake used per weight of lean body mass was applied (11, 12). The similar \( V_{O_{2\text{max}}} \) of the gender groups in the present investigation suggests that physical fitness was an unlikely explanation for differences in orthostatic tolerance between females and males.

As expected, LBNP elicited increased HR, peripheral resistance, leg volume, and catecholamines to levels comparable to those observed by others who employed similar techniques to test orthostatic responses (1, 2, 15, 16, 23, 24, 30, 37). It has been suggested that tolerance to progressive LBNP can be partially explained by differences in pre-LBNP Q reserves and higher compensatory increases in peripheral resistance to a given orthostatic stress (2, 6). These notions were not adequate to explain differences in LBNP tolerance between the gender groups in the present study, because equal pre-LBNP Q and greater increases in peripheral resistance to a given LBNP level did not protect against earlier onset of presyncope in the females. Also, the possibility that lower baseline systolic blood pressure in the females may have contributed to their earlier onset of orthostatic intolerance cannot be dismissed. However, this possibility seems unlikely because higher baseline arterial pressure in males compared with females, similar to the difference between gender groups of the present investigation, did not contribute significantly to higher G tolerance (28). Females had higher baseline HR and elicited greater tachycardic responses at equal LBNP. However, this reflex cardiac response was inadequate to maintain Q in the women compared with the men. Thus the results of the present study indicate that the rate of Q reduction may be a significant factor that contributed to earlier onset of hypotension in females in the present study.

Baroreceptor-mediated tachycardia provides a means to buffer transient changes in arterial blood pressure. Investigations using both human and animal models have demonstrated that carotid-cardiac baroreflex dysfunction is associated with less cardioacceleration and greater incidence of hypotension during orthostasis (4, 5, 10). A positive correlation has been reported between the magnitude of impairment of carotid-cardiac baroreflex function and incidence of syncope during passive standing (5). In the present study, lower LBNP tolerance was associated with attenuated carotid-cardiac baroreflex responsiveness in the female subjects compared with their male counterparts. The isolated carotid-cardiac baroreflex stimulus-response relationship in the women was shifted, such that a 33% lower maximum slope existed in the region of hypotension. This lesser responsiveness in carotid-cardiac baroreflex function was further verified by a lower \( \Delta \text{HR}/\Delta \text{MAP} \) during the Valsalva maneuver in the females compared with the males. This attenuated reflex response may have partly contributed to the reduced capacity of the females to buffer against transient reductions in blood pressure during LBNP.

The observation in this and other (30, 37) investigations that females demonstrated greater elevation in HR than males during graded LBNP has led to the hypothesis that vagal withdrawal rather than sympathetic activation may be a more important mechanism underlying blood pressure regulation in women (15). This hypothesis is consistent with the observation that an attenuated response of the vagally mediated carotid-cardiac baroreflex and total circulating NE at presyncope was associated with lower orthostatic tolerance in female subjects compared with males in the present study. A lower baseline HR variability and attenuated carotid-cardiac baroreflex responsiveness in the females compared with the males of the present study might suggest that vagal withdrawal from low baseline cardiac vagal tone represents a possible underlying mechanism for limited cardioacceleration in women.

Although lower cardiac baroreflex responsiveness was associated with earlier onset of presyncope in women, HR at presyncope in the female subjects did not differ from that observed in the males. This was especially surprising, because the women elicited less elevation of total circulating plasma NE than the men, suggesting that less sympathetic activation induced similar tachycardic response during LBNP in females. This difference in the sympathetic stimulus-HR response relationship between women and men could be explained by evidence of greater responsiveness of cardiac \( \beta \)-adrenoreceptors observed in the women (Fig. 5). Because blood pressure stimulus to arterial baroreceptors was similar between gender groups and cardiac baroreflex responses were smaller in females, it seems likely that the greater tachycardic response observed in the females during ISO infusion was primarily due to higher \( \beta \)-adrenoreceptor responsiveness.

The finding that HR at presyncope did not differ between women and men makes the interpretation regarding the contribution of vagally mediated baroreflex control of HR to blood pressure regulation less clear. An alternative method of interpreting the difference in baroreflex responsiveness between the two gender groups and its importance in maintenance of arterial pressure during hypotension is to calculate the change in Q that would be expected to occur when a given reduction in blood pressure elicits a given reflex change in HR (25). In the present study, when average stroke volume at presyncope was multiplied by the carotid baroreflex gain during a change in MAP from 100 (baseline) to 80 mmHg (presyncope), the unit change in Q was 105% greater in the men compared with the women (4.8 beats/min \( \times \) 48 ml/beat = 230 ml/min vs. 3.2 beats/min \( \times \) 35 ml/beat = 112 ml/min, for men and women, respectively). Therefore, despite small differences in the magnitude of the cardioacceleratory baroreflex response between groups, these calculations suggest that the baroreflex-mediated cardiac response in female subjects may have significantly reduced the capacity to provide adequate Q during LBNP.

Earlier onset of presyncope in our female subjects was associated with lower Q compared with males. The
capacity to maintain Q and systemic arterial pressure during an orthostatic challenge can be influenced by impaired venous return as a result of blood pooled in the lower body. The notion that females in the present study had lower venous return and cardiac filling compared with the males was supported by greater increases in thoracic impedance and greater fall in Q during LBNP in the women. On the basis of this observation, greater leg compliance and fluid accumulation during LBNP might be predicted for the females. Consistent with previous investigations (15, 23, 30), males of the present study demonstrated an average leg compliance 24% greater than the females and experienced greater fluid accumulation in their legs during LBNP compared with the females, as evidenced by a larger percentage increase in calf circumference. These observations dismiss the possibility that LBNP tolerance could be explained by differences in the quantity of blood sequestered in the legs alone. However, it is possible that females had lower venous return with less blood pooling in the legs by selectively sequestering the majority of blood in their abdominal region, inasmuch as pelvic blood pooling has been as much as sixfold greater in women compared with men at equal orthostatic challenge (38).

The capacity to increase total systemic peripheral resistance represents an important mechanism for buffering against the development of hypotension during an orthostatic challenge. Some data suggest that vasoactive responses of vascular adrenergic receptors were lower in women than men because men showed significant dose-related vasoconstriction to PE and vasodilation to Iso, whereas women did not (14). However, similar vasoactive responses to PE and Iso were found between females and males of the present study, suggesting that differences in vascular adrenergic receptor responsiveness did not contribute to lower orthostatic tolerance in females. It has also been suggested that females may have lower capacity to vasoconstrict, because increased TPR during LBNP was less in females compared with males (15). In contrast, several responses observed in the present study indicate that the capacity to vasoconstrict was not compromised in females. TPR at the onset of presyncope was similar for females and males in the present study. In addition, vasoconstriction responses during nonpresyncope levels of LBNP were substantially greater in the females compared with the males (Fig. 2, Table 3). The latter observation was further supported by similar or greater average response of increased FVR to cardiopulmonary baroreceptor stimulation in females compared with males (Fig. 5). A possible limitation for vasoconstriction in females based on the present data may be the degree to which women use their vasoconstrictive reserve (defined as the difference between peripheral resistance at baseline and presyncope) (13). Females and males in the present study should have had similar vasoconstrictive reserve, because their TPR and FVR at baseline and presyncope were similar. Because the vasoconstrictive response to LBNP in this investigation occurred at a faster rate in females, lower LBNP tolerance in females was associated with a greater elicitation of their maximal vasoconstrictive reserve at lower LBNP. It has been suggested that just before the point at which an orthostatic challenge is sufficient to elicit hypotension, compensatory mechanisms are usually operating at maximal capacity (32). If this is true, orthostatic tolerance of females may be limited by the inability to recruit further vasoconstriction from mechanisms that have reached their maximal capacity.

Circulating blood volume has a profound effect on arterial pressure during orthostasis (1, 3, 7, 25, 27, 28). Subjects with reduced vascular volumes exhibit subnormal filling pressures and may be shifted to the steep portion of their Frank-Starling curve, where capacity to buffer orthostatic reductions in central blood volume is limited (25). Earlier onset of presyncope in female subjects of the present study was associated with a greater fall in Q compared with males. It is possible that lower relative circulating blood volume in the females contributed to more rapid reduction of cardiac filling and subsequent failure to maintain blood pressure at lower levels of LBNP.

Low blood volume in females compared with the males of the present investigation could also have contributed to earlier saturation of vasoconstriction during LBNP, because hypovolemia elicits greater vascular resistance for equal reductions in venous pressure (36). This notion is consistent with the observation that females in this study demonstrated substantially greater vasoconstriction at similar levels of LBNP compared with the males and a greater average response (slope) for increased FVR to cardiopulmonary baroreceptor stimulation (Figs. 2 and 5). These responses have been interpreted to represent a greater utilization of vasoconstrictive reserve, such that maximal pressor response is attained at a lesser reduction in central blood volume (36). It is therefore reasonable that predisposition for earlier onset of presyncope in female subjects may partly result from a relative hypovolemia that limited cardiac filling and the capacity to increase systemic resistance.

Total circulating plasma NE, an index of sympathetic activity (18), is increased during orthostasis, and higher Elevations are associated with increased orthostatic tolerance (2, 13, 17). In the present study, the increase in total circulating plasma NE from baseline to presyncope was greater in males compared with females, whereas changes in total circulating Epi were similar between the gender groups. Therefore, it appeared that neuronal release of catecholamines was attenuated in females, which may limit compensatory elevations in cardiac contractility, HR, and systemic peripheral resistance required to defend against the onset of hypotension and syncope.

In summary, LBNP tolerance was significantly lower in females than males who matched for age and aerobic fitness. At presyncope, HR and peripheral vascular resistance were similar in both groups. Presyncope predisposition in females was associated with less HR response to carotid baroreceptor stimulation, lower baseline cardiac vagal (parasympathetic) activity,
greater decline in $Q$ induced by LBNP, increased $\beta_1$-adrenoreceptor responsiveness, greater vasoconstriction under equal LBNP, lower levels of total circulating NE at presyncope, and lower blood volume. The results of this investigation support the hypothesis that women have attenuated responsiveness in mechanisms that underlie blood pressure regulation under orthostatic challenge relative to men.

**Perspectives**

The observation that the capacity to buffer against development of hypotension and orthostatic responsiveness is significantly less in women compared with men has important implications for selection and training of females for aerial combat missions that require exposure to high sustained $+G_z$ accelerations. The failure of women to demonstrate increased stroke volume, $Q$ and the protection against orthostatic hypotension after high-G training compared with men was associated with lower tracking performance during simulated air-to-air combat at high G (9). These results provided evidence that blood pressure regulation was associated with, and may be an important underlying mechanism for, cognitive task performance during high-G maneuvers. Perhaps as important is the possible implication that female pilots may have less physiological potential to adapt their cardiovascular functions during training to support optimal performance during aerial combat. If less responsive mechanisms of blood pressure regulation, such as those observed in the females of the present study, fail to respond or adapt adequately to $+G_z$ exposure, combat training and performance of female pilots may be significantly limited. In addition, data from the present investigation suggest that, in addition to the importance of well-fitted garments, the design of anti-G suits for female pilots should include greater counterpressure applied to the pelvic region with less required around the legs compared with men. Whether crew selection, training, or technological life support systems can be designed to enhance these physiological functions could be critical to the potential future of female pilots.

The author thanks the following individuals for their part in making this project a success: Dr. Sheryl Wright at University of Texas Health Sciences Center at San Antonio; Drs. Sandra Oswald, James Slauson, Joseph Deering, Theodore Arevalo, Jeb Pickard, James Slauson, Joseph Deering, Theodore Arevalo, Jeb Pickard, Dr. Sandra Oswald, James Slauson, Joseph Deering, Theodore Arevalo, Jeb Pickard, James Slauson, Joseph Deering, Theodore Arevalo, Jeb Pickard, Mss. Patricia Beightol, and D. L. Eckberg, Inc., for engineering support; Richard Owens, Russell Woods, Gary Muniz, and Jim Lutze at Rothe Development, Inc., for laboratory support; Cullen Hardy, and William Kruyer at the Physiology Research Branch, Clinical Sciences Division, Armstrong Laboratory for medical support during experiments and collection of blood samples; Marion Merz at Binetics Corp., Kennedy Space Center for analysis of plasma and hormone samples; Dr. Marty Javors University of Texas Health Sciences Center at San Antonio for analysis of plasma catecholamines; and the subjects for their cheerful cooperation.

This project was supported in part by a grant administered under the Defense Women's Health Research Program.

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**REFERENCES**