

Hemodynamics of orthostatic intolerance: implications for gender differences

Qi Fu, Armin Arbab-Zadeh, Merja A. Perhonen, Rong Zhang,
Julie H. Zuckerman, and Benjamin D. Levine

Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas,
and the University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75231

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Fu, Qi, Armin Arbab-Zadeh, Merja A. Perhonen, Rong Zhang, Julie H. Zuckerman, and Benjamin D. Levine. Hemodynamics of orthostatic intolerance: implications for gender differences. *Am J Physiol Heart Circ Physiol* 286: H449–H457, 2004. First published October 2, 2003; 10.1152/ajpheart.00735.2002.—Women have a greater incidence of orthostatic intolerance than men. We hypothesized that this difference is related to hemodynamic effects on regulation of cardiac filling rather than to reduced responsiveness of vascular resistance during orthostatic stress. We constructed Frank-Starling curves from pulmonary capillary wedge pressure (PCWP), stroke volume (SV), and stroke index (SI) during lower body negative pressure (LBNP) and saline infusion in 10 healthy young women and 13 men. Orthostatic tolerance was determined by progressive LBNP to presyncope. LBNP tolerance was significantly lower in women than in men (626.8 ± 55.0 vs. 927.7 ± 53.0 mmHg \times min, $P < 0.01$). Women had steeper maximal slopes of Starling curves than men whether expressed as SV (12.5 ± 2.0 vs. 7.1 ± 1.5 ml/mmHg, $P < 0.05$) or normalized as SI (6.31 ± 0.8 vs. 4.29 ± 0.6 ml \cdot m $^{-2}$ \cdot mmHg $^{-1}$, $P < 0.05$). During progressive LBNP, PCWP dropped quickly at low levels, and reached a plateau at high levels of LBNP near presyncope in all subjects. SV was 35% and SI was 29% lower in women at presyncope (both $P < 0.05$). Coincident with the smaller SV, women had higher heart rates but similar mean arterial pressures compared with men at presyncope. Vascular resistance and plasma norepinephrine concentration were similar between genders. We conclude that lower orthostatic tolerance in women is associated with decreased cardiac filling rather than reduced responsiveness of vascular resistance during orthostatic challenges. Thus cardiac mechanics and Frank-Starling relationship may be important mechanisms underlying the gender difference in orthostatic tolerance.

orthostatic hypotension; stroke volume; vascular resistance; pulmonary capillary wedge pressure; lower body negative pressure

IN HUMANS, TOLERANCE TO ORTHOSTATIC stress requires the successful integration of multiple elements of cardiovascular control. Syncope may occur when there is an abnormally large postural decrease in central blood volume, cardiac filling pressure, stroke volume (SV), and cardiac output (CO), or inadequate neurohumoral reflex responses to orthostasis, primarily tachycardia and vasoconstriction (2). It has been noted that women have lower orthostatic tolerance than men (7, 15, 23, 35, 50). Specific mechanisms underlying this difference have not been totally elucidated and are probably multifactorial.

One recent study (50) on astronauts suggested that the incidence of orthostatic presyncope after spaceflight was greatest in women, and this was ascribed to a combination of

inherently lower resistance and relative hypoadrenergic responses. However, evidence for this conclusion was not definitive, because the results were obtained from a very small number of subjects analyzed retrospectively. Frey et al. (13, 14) proposed that women might respond to orthostatic challenges with more prominent vagal withdrawal, whereas men might respond with greater sympathetic stimulation to the peripheral vasculature. This notion was supported by the observation that women demonstrated greater elevations in heart rate (HR) than men (7, 35, 51), but was not consistent with the finding that peripheral vascular resistance was similar for both genders at onset of presyncope (7).

An alternative interpretation is that greater elevation in HR in women is simply because of greater reduction in SV, rather than a fundamentally different strategy of cardiovascular regulation during orthostasis. SV is the key variable in the HR-SV-total peripheral resistance (triple-product) relation that is directly affected by gravity (28), and it is a major determinant of flow in baroreceptive arteries, which modulates baroreceptor activity (18). SV changes translate into arterial pulse amplitude and pressure changes, and these clearly modulate arterial baroreceptor activity (1, 4). Moreover, SV is a direct, linear function of central blood volume and left ventricular end-diastolic volume (LVEDV) and thereby accurately reflects the stimulus to the myriad of receptor populations termed “cardio-pulmonary” (42).

We previously demonstrated that changes in SV during lower body negative pressure (LBNP) can be one of the predictors of LBNP tolerance (28); in addition, the left ventricular (LV) pressure-volume and Frank-Starling relations are mechanical nonautonomic causes of orthostatic intolerance in athletes (29). Therefore, we reasoned that the regulation of SV including cardiac load, size, and performance might be different between men and women, and could contribute to the gender difference in orthostatic tolerance.

The purpose of the present study was to test the hypothesis that the susceptibility to orthostatic intolerance in women is related to hemodynamic effects on regulation of cardiac filling rather than to a reduced responsiveness of vascular resistance during orthostatic stress. To accomplish this objective, we constructed Frank-Starling curves from pulmonary capillary wedge pressure (PCWP) and SV as well as stroke index during LBNP and rapid saline loading. Orthostatic tolerance was determined by progressive LBNP to presyncope. For the first time, we monitored PCWP during progressive LBNP contin-

Address for reprint requests and other correspondence: B. D. Levine, Institute for Exercise and Environmental Medicine, 7232 Greenville Ave., Suite 435, Dallas, TX 75231 (E-mail: BenjaminLevine@texashealth.org).

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ously, including before the onset of syncope. Additionally, hemodynamic variables and plasma catecholamines were measured during the experiment.

MATERIALS AND METHODS

Subjects

Ten women and thirteen men matched for age and fitness were recruited in this study. All were young, healthy, normotensive individuals. No subject smoked, used recreational drugs, or had significant medical problems. None was an endurance-trained athlete (28), and subjects were excluded if they exercised for >30 min/day more than three times per week (either dynamic or static exercise). No woman was pregnant, and none was using oral contraceptives during the experiments. Subjects were screened with a careful history, physical examination, and ECG. All subjects were informed of the purpose and procedures used in the study and gave their written informed consent approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas. A summary of the descriptive data for the subjects in both groups is presented in Table 1.

Measurements

HR and blood pressure. HR was monitored continuously from the ECG (Hewlett-Packard), and beat-by-beat arterial pressure was derived by finger photoplethysmography (Finapres; Ohmeda). Arm blood pressure (BP) was measured intermittently by electrophygmomanometry (SunTech Medical Instruments) with a microphone placed over the brachial artery to detect Korotkoff sounds. Changes in calf volume during each LBNP stage were measured with a strain gauge placed around the point of maximum girth of the calf in 12 subjects (1 female, 11 males) in another study during the same orthostatic tolerance test. Among these subjects, eight (1 woman and 7 men) participated in this study. Percent changes in calf volume (ml/100 ml) were calculated from the circumference changes.

CO. CO was measured with a modification of the acetylene rebreathing technique by using acetylene as the soluble gas and helium as the insoluble gas (48). With this technique, pulmonary blood flow is calculated from the disappearance rate of acetylene in expired air, measured with a mass spectrometer (Marquette), after adequate mixing in the lung has been confirmed by a stable helium concentration. This method has been validated in our laboratory against standard invasive techniques, including thermodilution and direct Fick (38). CO was measured at baseline, -15, -30, -40, -60, and -80 mmHg LBNP. SV was calculated from CO and the HR measured during rebreathing.

Cardiac filling pressure. A 6-Fr balloon-tipped, flow-directed pulmonary arterial catheter (Edwards Swan-Ganz; Baxter) was placed under fluoroscopic guidance through a right antecubital vein into the

pulmonary artery. With the balloon inflated, the catheter was advanced into the pulmonary capillary wedge position, which was confirmed both fluoroscopically and by the presence of characteristic pressure waveforms. Right atrial pressure (RAP) was measured at the proximal part of the catheter. Pulmonary artery pressure (PAP) was measured with the balloon deflated. PCWP was determined visually at end expiration with the balloon inflated and was used as an estimation of LV end-diastolic pressure (29, 31). All intracardiac pressures were referenced to atmospheric pressure, with the pressure transducer (Transpac IV; Abbott) zero reading set at 5 cm below the sternal angle in the supine position. Pressure waveforms were amplified (Hewlett-Packard 78534A and Astromed ASC909) and displayed on a strip-chart recorder (Astromed MT 95000) with ≤ 0.5 -mmHg resolution.

Plasma measurements. Blood samples were drawn from the RA part of the Swan-Ganz catheter for measurements of plasma catecholamines at baseline, -15 and -30 mmHg LBNP, and immediately (within 15 s) after termination of the maximum LBNP when the subjects became presyncopal. Plasma norepinephrine and epinephrine concentrations were measured by an independent laboratory by using high-precision liquid chromatography according to standardized procedures. Plasma volume was measured with the standard Evans blue dye technique (12). Total blood volume was calculated from the plasma volume and peripheral venous hematocrit measurements.

Protocols

All experiments were performed in the morning ≥ 2 h after a light breakfast and >12 h after the last caffeinated or alcoholic beverage, in a quiet, environmentally controlled laboratory with an ambient temperature of 25°C. The subject was placed in a Plexiglas LBNP tank sealed at the level of the iliac crests in the supine position. Suction was provided by a vacuum pump, controlled with a variable autotransformer, and calibrated against a mercury manometer. After at least a 30-min baseline period of quiet rest, LBNP was begun at -15 mmHg for 5 min, then increased to -30 mmHg for 5 min, and followed by a recovery for 5 min. Measurements of PCWP, CO (and therefore SV), HR, and BP were made at each level. This protocol was carried out to decrease cardiac filling for constructing Frank-Starling curves, as reported previously (29, 31).

After a sufficient recovery period (≥ 10 min), baseline measurements were repeated to confirm a return to the hemodynamic steady state. Maximal orthostatic tolerance was determined while the subject was supine by using progressive LBNP to presyncope. LBNP was begun at -15 mmHg for 5 min, then increased to -30 and -40 mmHg for 5 min each, followed by an increase in LBNP by -10 mmHg every 3 min until signs or symptoms of presyncope were achieved. Presyncope was defined as a decrease in systolic BP to <80 mmHg; a decrease in systolic BP to <90 mmHg associated with symptoms of lightheadedness, nausea, sweating, or diaphoresis; or progressive symptoms of presyncope accompanied by a request from the subject to discontinue the test. A true hemodynamic end point was reached in all the tests in the present study. The recovery period lasted for 5 min. A cumulative stress index was calculated for this specific protocol by adding the product of negative pressure and duration at each level of LBNP and was used as a continuous measure of orthostatic tolerance (29, 31).

After the maximal LBNP test, a 20-min break was given before the saline loading was begun. After repeat baseline measurements (to confirm a return to the hemodynamic steady state), cardiac filling was increased by a rapid (100 ml/min) infusion of warm (37°C) isotonic saline. Measurements were repeated after 15 and 30 ml/kg saline had been infused. This protocol was performed to increase cardiac filling for constructing Frank-Starling curves (29, 31).

Data Analysis

Frank-Starling curves. Frank-Starling curves were created by computer fit of the best polynomial regression through the grouped means

Table 1. Subject characteristics

	Men	Women
<i>n</i>	13	10
Age, yr	25.5 ± 1.4	29.6 ± 1.9
Height, cm	178.3 ± 0.9	168.8 ± 2.0‡
Weight, kg	80.3 ± 2.2	62.0 ± 1.8‡
Body surface area, m ²	1.99 ± 0.03	1.70 ± 0.03‡
Plasma volume, liter	3.05 ± 0.06	2.60 ± 0.14‡
Normalized plasma volume, ml/kg	38 ± 1	42 ± 2
Total blood volume, liter	4.98 ± 0.15	3.94 ± 0.20‡
Normalized blood volume, ml/kg	63 ± 3	64 ± 3
Hematocrit, %	44.00 ± 0.61	38.90 ± 0.67‡

Values are means ± SE; *n*, number of subjects. ‡*P* < 0.01 compared with men by unpaired *t*-test.

for PCWP and SV in both genders. To account for the differences in baseline values of SV between men and women, Frank-Starling curves were also created through the grouped means for PCWP and stroke index in both groups. To quantify the maximal steepness of the Starling curve, the change in SV and stroke index relative to a change in PCWP was calculated for each transition in cardiac filling from -30 mmHg LBNP through 30 ml/kg of saline infusion. The maximal value for each individual subject was identified and then group means were calculated.

Hemodynamic calculations. Mean arterial pressure (MAP) was calculated as $[(SBP-DBP)/3] + DBP$, where SBP and DBP are systolic and diastolic BP, respectively. Systemic vascular resistance (SVR) was calculated as $[(MAP-RAP)/CO] \times 80$, and pulmonary vascular resistance (PVR) was calculated as $[(PAP-PCWP)/CO] \times 80$ (each is expressed as $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$).

Statistical Analysis

Data are expressed as means \pm SE. Subjects' characteristics, comparisons at baseline, and maximal reductions in SV and stroke index during changes in PCWP in the Frank-Starling curves between the genders were made with the use of unpaired *t*-tests. Baseline and progressive LBNP values within the group were compared by using one-way repeated-measures ANOVA, and with Bonferroni corrected *t*-test post hoc for multiple comparisons. Between-group comparisons during LBNP were compared by two-way, repeated-measures ANOVA for the effects of gender and stage of LBNP, and with Student-Newman-Keuls method post hoc for multiple comparisons. The relationship between changes in SV and stroke index and changes in PCWP during progressive LBNP (-15 , -30 , -40 , and -60 mmHg) was determined by linear regression analysis for each subject, and the slopes for the gender groups were compared with the use of unpaired *t*-test. In addition, linear regressions were calculated from mean values of plasma norepinephrine concentration and SVR to the mean values of SV and stroke index at baseline, -15 , and -30 mmHg LBNP for both groups. All statistical analyses were performed with a personal computer-based analysis program (SigmaStat, SPSS, Chicago, IL). A *P* value of < 0.05 was considered statistically significant.

RESULTS

Physical Characteristics

Table 1 summarizes the descriptive data for both groups. The two groups did not differ in age, but differed in height, weight, body surface area, plasma volume, total blood volume, and hematocrit (all $P < 0.01$). However, when normalized to the body weight, differences in plasma volume and total blood volume were eliminated. Resting HR was not significantly different between the groups (72 ± 2 in women vs. 69 ± 2 beats/min in men, $P > 0.05$). But women had lower baseline MAP (79 ± 2 vs. 86 ± 2 mmHg, $P < 0.05$) and smaller baseline SV (83 ± 4 vs. 101 ± 5 ml, $P < 0.05$) compared with men. Resting CO did not significantly differ between the genders (6.0 ± 0.2 in women vs. 6.9 ± 0.3 l/min in men, $P > 0.05$). Both resting stroke index (48.9 ± 2.2 vs. 50.5 ± 3.0 ml/m², $P > 0.05$) and cardiac index (3.51 ± 0.13 vs. 3.44 ± 0.19 l \cdot min⁻¹ \cdot m⁻², $P > 0.05$) were similar in women and men.

Frank-Starling Curves

Figure 1 depicts Frank-Starling relationships in both groups. PCWP decreased during LBNP when compared with the baseline value, and it increased during saline loading (all $P < 0.05$). At any given LBNP level, SV (Fig. 1A) and stroke index (Fig. 1B) were smaller than at baseline (both $P < 0.05$). Twelve

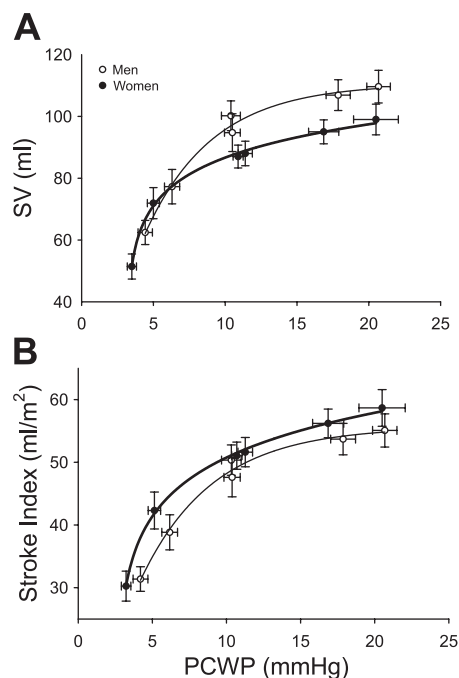


Fig. 1. Frank-Starling curves in men and women. Values are means \pm SE, demonstrating Starling curves relating pulmonary capillary wedge pressure (PCWP) to stroke volume (SV; A) and stroke index (B) in both groups. Curve is derived from values obtained during lower body negative pressure [LBNP; reduced left ventricular (LV) filling] and saline infusion (increased LV filling). Two middle points present 2 baseline values before LBNP and saline infusion. Curves are created by computer fit of the best polynomial regression through the mean values for each group.

subjects (10 men, 2 women) had their biggest drop in SV between baseline and -15 mmHg LBNP, whereas 11 subjects (3 men, 8 women) had the biggest drop between -15 and -30 mmHg LBNP. For all women, the maximum slope of the Frank-Starling curve (namely, $\Delta\text{SV}/\Delta\text{PCWP}$ and $\Delta\text{stroke index}/\Delta\text{PCWP}$) was obtained between -15 and -30 mmHg LBNP. However, for the men, 9 of them had their maximum slope between -15 and -30 mmHg LBNP, whereas 4 had the maximum slope between baseline and -15 mmHg LBNP. The maximum slope of the Frank-Starling curve was significantly steeper in women than in men ($\Delta\text{SV}/\Delta\text{PCWP}$ was 12.5 ± 2.0 in women and 7.1 ± 1.5 ml/mmHg in men, whereas $\Delta\text{stroke index}/\Delta\text{PCWP}$ was 6.31 ± 0.8 in women and 4.29 ± 0.6 ml \cdot m⁻² \cdot mmHg⁻¹ in men; both $P < 0.05$). The functional consequence of this concept is that during an orthostatic challenge, a similar decrease in PCWP (for example, ~ 2 mmHg decrease in PCWP from -15 to -30 mmHg LBNP) would be associated with a greater reduction in SV and stroke index in women (~ 25 ml and 30% of the baseline value of SV; ~ 12.1 ml/m² and 21% of the baseline value of stroke index) than in men (~ 14 ml and 14% of the baseline value of SV; ~ 8.5 ml/m² and 15% of the baseline value of stroke index).

Cardiovascular Responses to Progressive LBNP

The maximum LBNP tolerance time was significantly shorter (18.0 ± 1.2 vs. 23.3 ± 0.7 min, $P < 0.01$) and the cumulative stress index was markedly smaller (626.8 ± 55.0 vs. 927.7 ± 53.0 mmHg \times min, $P < 0.01$) in the women compared with the men. SV and CO gradually decreased

during progressive LBNP; both variables were lower for the women than men at equal levels of LBNP greater than -30 mmHg (Fig. 2, C and D, both $P < 0.05$). SV was 35% lower in women compared with men at presyncope ($P < 0.05$). Stroke index and cardiac index also gradually decreased during progressive LBNP in both men and women (Fig. 2, E and F). Stroke index was significantly lower in women at -60 mmHg LBNP compared with men ($P < 0.05$). Cardiac indexes between genders were similar. HR gradually increased and MAP progressively decreased in all the subjects during progressive LBNP (Fig. 2, A and B). Coincident with the smaller SV, HR was higher and MAP was lower at equal levels of LBNP in women compared with men (both $P < 0.05$). At presyncope, women had a higher HR, but similar MAP compared with men.

To determine whether the difference in resting SV was influencing the SV response to maximal LBNP, we identified nine pairs of healthy men and women from all previous studies in our laboratory in which the same maximal LBNP protocol was performed, matched for resting SV. Eight of the men and five of the women came from the present study. Their data are shown in Fig. 3, which reveals identical absolute SVs at baseline and during low-level LBNP. Four of each pair of these subjects also had MRI measures of LV mass and LVEDV as previously described (40). Despite having the same resting supine SV (86 ± 6 vs. 87 ± 6 ml), men had larger LV masses

(172 ± 4 vs. 118 ± 6 g) and accomplished the same SV from a larger LVEDV (129 ± 2 vs. 92 ± 5 ml). Most importantly, similar to data for the main experimental cohort, during higher levels of LBNP, the SVs of these women decreased to a greater degree than the men, accompanied by a proportionally greater HR (Fig. 3, A and B, both $P < 0.05$).

Decrease in PCWP from baseline to -15 mmHg LBNP was greater in women than men (-6.7 ± 0.4 vs. -4.0 ± 0.4 mmHg, $P < 0.05$). PCWP and RAP dropped quickly at -15 and -30 mmHg LBNP, then more slowly, and reached a plateau at high levels of LBNP to presyncope; these responses were not different between the genders (Fig. 4). To determine whether the plateau in cardiac filling pressure was due to a plateau in peripheral pooling during LBNP, we analyzed the change in calf volume during the identical LBNP protocol derived from a previous experiment in which eight of these subjects from the present study participated. Calf volume increased linearly during progressive LBNP and reached a peak at presyncope (1.14 ± 0.18 , 2.07 ± 0.25 , 2.86 ± 0.32 , 3.52 ± 0.38 , 4.09 ± 0.42 , 4.39 ± 0.41 , and $5.2 \pm 0.66\%$ at -15 , -30 , -40 , -50 , -60 , -70 , and -80 mmHg LBNP, respectively), with no evidence for a plateau in peripheral pooling.

Averaged changes in SV and stroke index in relation to changes in PCWP during progressive LBNP (-15 , -30 , -40 ,

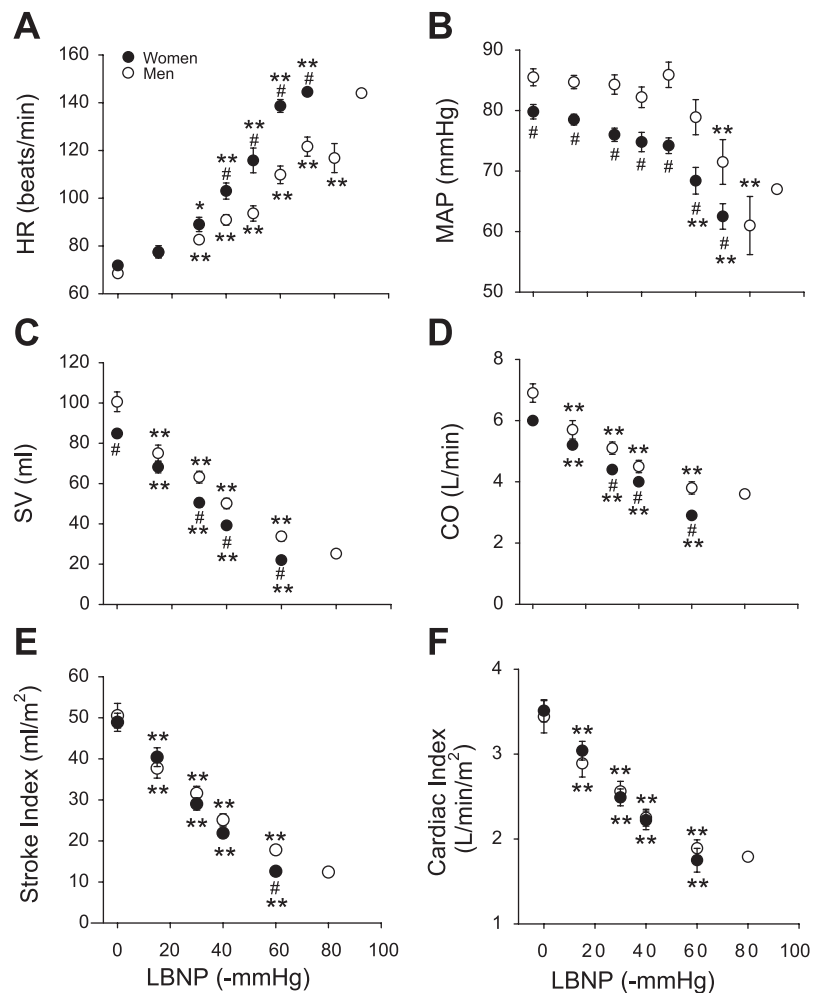


Fig. 2. Cardiovascular responses during progressive LBNP to presyncope in men and women. Values are means \pm SE of heart rate (HR; A), mean arterial pressure (MAP; B), SV (C), cardiac output (CO; D), stroke index (E), and cardiac index (F). In the men, the number of the subjects is 13 for each data point at 0 (baseline), -15 , -30 , -40 , -50 , and -60 mmHg LBNP but decreased to 11 for the data point at -70 mmHg LBNP (because of subject drop-out due to presyncope); to 4 for the data point of HR and MAP, but 1 for the data point of SV, CO, stroke index, and cardiac index at -80 mmHg LBNP; and to 1 for the data point of HR and MAP at -90 mmHg LBNP. In the women, the number of the subjects is 10 for each data point at 0, -15 , -30 , and -40 mmHg LBNP; decreased to 7 for the data point at -50 mmHg LBNP; to 6 for the data point at -60 mmHg LBNP; and to 2 for the data point at -70 mmHg LBNP. * $P < 0.05$ and ** $P < 0.01$ compared with baseline within the group; # $P < 0.05$ compared with men.

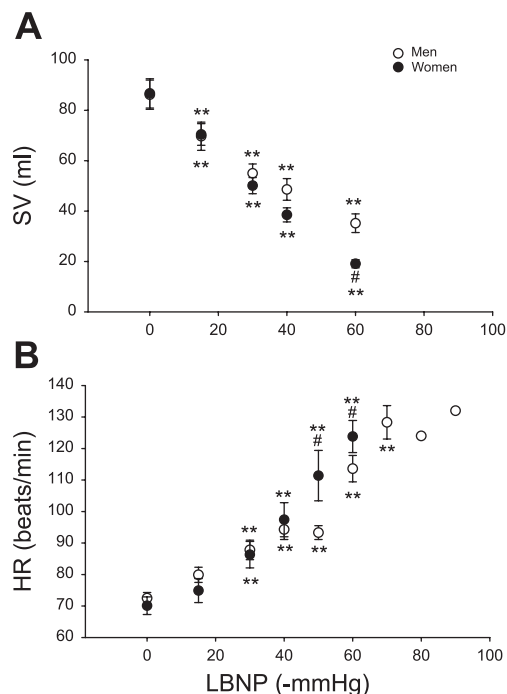


Fig. 3. Matched resting SV (A) and HR (B) in healthy young men and women, and their responses to progressive LBNP to presyncope. Values are means \pm SE. In men, the number of the subjects is 9 for each data point at 0 (baseline), -15, -30, and -40 mmHg LBNP but decreased to 7 for the data point at -60 mmHg LBNP (because of subject drop-out due to presyncope). In women, the number of the subjects is 9 for each data point at 0 (baseline), -15, -30, and -40 mmHg LBNP but decreased to 3 for the data point at -60 mmHg LBNP. ** $P < 0.01$ compared with baseline within the group, # $P < 0.05$ compared with men.

and -60 mmHg) are plotted in Fig. 5. The slope of the line relating SV and stroke index to PCWP was significantly steeper in women compared with men (14.3 ± 3.7 vs. 7.8 ± 1.2 ml/mmHg, and 8.4 ± 2.8 vs. 4.3 ± 0.5 ml \cdot m $^{-2}$ \cdot mmHg $^{-1}$, both $P < 0.05$), indicating a greater reduction in SV and stroke index in women for a change in PCWP during an orthostatic challenge.

SVR and PVR gradually increased during progressive LBNP, reaching a peak at presyncope. There was no gender difference in vascular resistance responses, although the increases in SVR and PVR reached significance in men sooner than it did in women (Fig. 6, A and B). Plasma norepinephrine concentration also gradually increased during progressive LBNP and reached a peak at presyncope, and the responses were not different between the men and women (Fig. 7A). Plasma epinephrine concentration was lower in women than men at maximal LBNP level (Fig. 7B).

To compare the interplay between the stimulus and response during orthostatic challenges in men and women, plasma norepinephrine concentration and SVR were plotted as functions of SV and stroke index at baseline, -15, and -30 mmHg LBNP in both groups. Average slopes of plasma norepinephrine concentration responses to changes in SV and stroke index were similar between men and women (Fig. 8, A and B). Average slopes of SVR responses to changes in SV and stroke index were also similar between the genders (Fig. 8, C and D).

DISCUSSION

Major findings from the present study are: 1) LBNP tolerance was significantly lower in women than men; 2) women had a steeper maximal slope of the Frank-Starling curve than men; 3) at presyncope, SV and stroke index were lower in women compared with men; 4) vascular resistance responses and plasma norepinephrine concentrations were similar in both groups during progressive LBNP to presyncope; and 5) PCWP dropped quickly at low levels of LBNP, then more slowly, and reached a plateau at high levels of LBNP near presyncope in all the subjects. Thus our results support the hypothesis that orthostatic intolerance in women is related to a decreased cardiac filling rather than to a reduced responsiveness of vascular resistance during an orthostatic challenge.

The Frank-Starling Relation and Its Implication for Orthostatic Intolerance in Women

The relationship between SV and LV end-diastolic pressure, namely, the Frank-Starling mechanism, is a key determinant governing the magnitude of the decrease in SV during orthostatic stress in humans (27, 29, 41). Orthostatic intolerance has been found almost always to be associated with a reduced SV during orthostasis, especially after an actual or simulated microgravity exposure (3, 27–29, 31). Previous work from this laboratory demonstrated that the heart became smaller and less distensible after 2 wk of head-down bed rest, resulting in a steeper Frank-Starling relationship, and leading to an excessive reduction in SV during orthostasis (31). This remodeling after

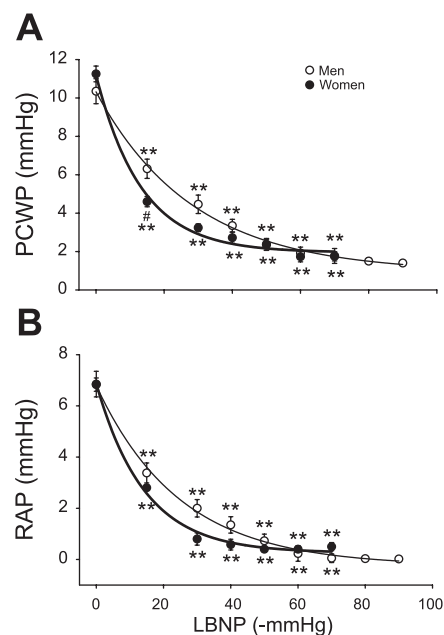


Fig. 4. PCWP (A) and right atrial pressure (RAP, B) in response to progressive LBNP to presyncope in men and women. Values are means \pm SE. In the male group, the number of the subjects is 13 for each data point at 0 (baseline), -15, -30, -40, -50, and -60 mmHg LBNP but decreased to 11 for the data point at -70 mmHg LBNP (because of subject drop-out due to presyncope), to 2 for the data point at -80 mmHg LBNP, and to 1 for the data point at -90 mmHg LBNP. In women, the number of the subjects is 6 for each data point at 0 (baseline), -15, -30, and -40 mmHg LBNP but decreased to 5 for the data point at -50 and -60 mmHg LBNP and to 2 for the data point at -70 mmHg LBNP. ** $P < 0.01$ compared with baseline within the group, # $P < 0.05$ compared with men.

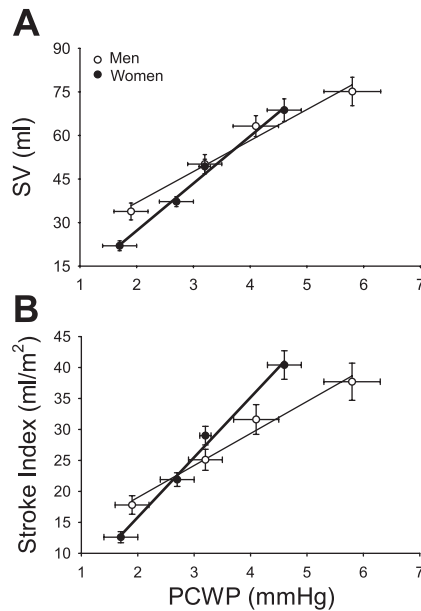


Fig. 5. Relationships between the changes in SV (A) and stroke index (B) to the changes in PCWP during progressive LBNP (-15 , -30 , -40 , and -60 mmHg) in men and women. Linear regressions are calculated from mean values. For PCWP vs. SV, the linear equation for the women is $y = 16.3x - 5.4$ ($r^2 = 0.992$) and for the men is $y = 10.7x + 12.2$ ($r^2 = 0.987$). For PCWP vs. stroke index, the linear equation for the women is $y = 9.7x - 3.5$ ($r^2 = 0.992$) and for the men is $y = 5.2x + 8.7$ ($r^2 = 0.980$).

bed rest was not observed with equivalent degrees of acute hypovolemia induced by diuresis in the same subjects (41). Although both interventions resulted in a reduced SV during orthostatic challenges, this reduction was greater after bed rest than acute diuresis, associated with a greater impairment of orthostatic tolerance (41).

In the present study, we found that women had a steeper maximal slope of their Frank-Starling curves compared with men, producing a diminished SV for any given cardiac filling pressure during progressive LBNP, similar to that observed after bed rest. This reduced SV in women was accompanied by a greater increase in HR. Thus the relative tachycardia in women may be explained as an appropriate reflex response to a smaller SV, rather than a fundamentally different strategy of BP regulation. This situation is therefore analogous with that of bed rest or spaceflight in which a reduced SV during orthostatic stress is accompanied by proportionally greater increases in HR and sympathetic nerve activity (30, 39). The unifying physiology in all these situations appears to be a reduced SV during orthostatic stress producing greater unloading of cardiac and arterial baroreceptors (1, 4).

Although MAP was lower at baseline as well as at each level of LBNP in women, this baseline difference did not appear to account for their earlier occurrence of presyncope. For both men and women, MAP remained relatively stable during progressive LBNP until hemodynamic collapse and prominent hypotension occurred suddenly. There was not a threshold BP that was reached earlier in women, but rather a neurally mediated event, presumably sympathetic withdrawal (20, 25, 49), that occurred when the heart was markedly unloaded.

Gender-specific factors can affect cardiac load, size, and performance (9, 34, 44). For example, LV anatomy and func-

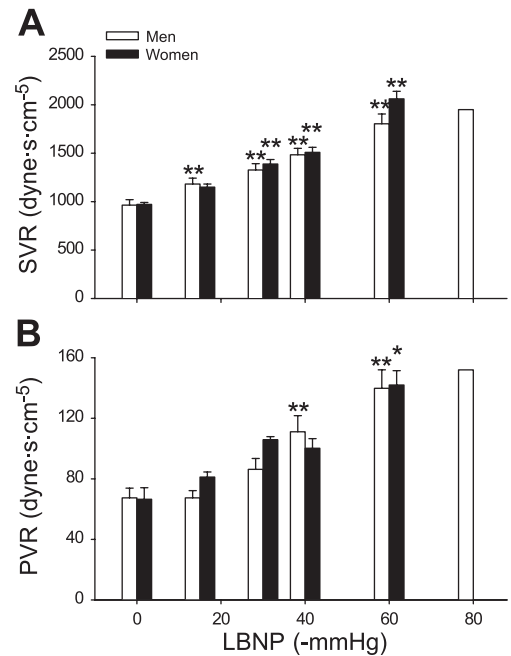


Fig. 6. Systemic and pulmonary vascular resistance (SVR and PVR; A and B) in response to progressive LBNP to presyncope in men and women. Values are means \pm SE. The number of the subjects in each group is the same as presented in Fig. 3. * $P < 0.05$ and ** $P < 0.01$ compared with baseline within the group.

tion are different between normotensive women and men (19, 32, 47). A smaller LV chamber seen in women was suggested to be associated with a higher systolic elastance (43) but a lower diastolic compliance (21). We observed similar differences in our subset of men and women matched for resting SV:

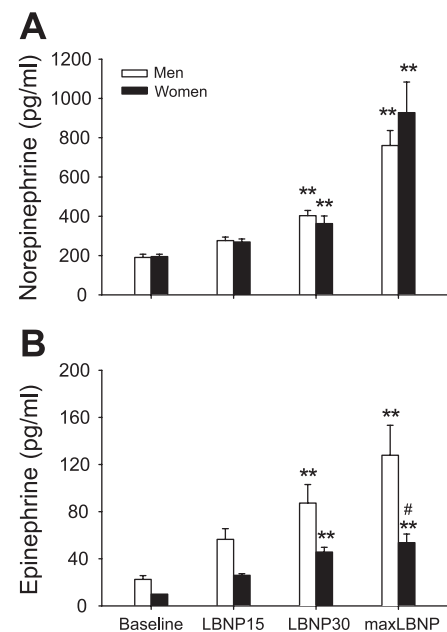


Fig. 7. Plasma norepinephrine (A) and epinephrine concentration (B) in response to progressive LBNP to presyncope in men and women. Values are means \pm SE. The number of the subjects in each group is the same as presented in Fig. 3. LBNP15, -15 mmHg LBNP; LBNP30, -30 mmHg LBNP; maxLBNP, maximal LBNP. ** $P < 0.01$ compared with baseline within the group, # $P < 0.05$ compared with men.

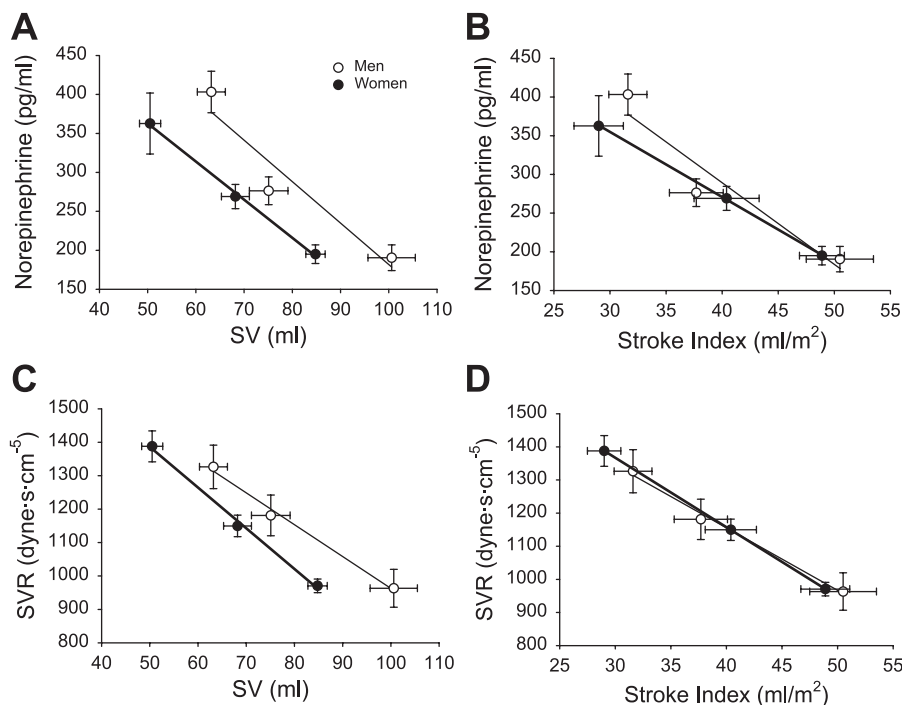


Fig. 8. Relationships between the changes in plasma norepinephrine concentration and SVR to the changes in SV and stroke index at baseline, -15, and -30 mmHg LBNP in men and women. Linear regressions are calculated from mean values. For SV vs. norepinephrine (A), the linear equation for women is $y = -4.9x + 607.5$ ($r^2 = 0.998$) and for men is $y = -5.3x + 713.6$ ($r^2 = 0.902$). For stroke index vs. norepinephrine (B), the linear equation for women is $y = -8.4x + 607.4$ ($r^2 = 1.000$) and for men is $y = -10.6x + 711.5$ ($r^2 = 0.905$). For SV vs. SVR (C), the linear equation for women is $y = -12.2x + 1,995.5$ ($r^2 = 0.996$) and for men is $y = -9.5x + 1,915.6$ ($r^2 = 0.992$). For stroke index vs. SVR (D), the linear equation for women is $y = -21.0x + 1,996.0$ ($r^2 = 1.000$) and for men is $y = -18.9x + 1,910.9$ ($r^2 = 0.993$).

LV mass and LVEDV were smaller in the women. It is possible that the smaller and less distensible LV in women may increase their sensitivity to fluid shifts. Moreover, they may reach a limit below which end-systolic volume cannot be further reduced to maintain SV in the face of steadily declining LVEDV. In addition to the gender-related structural and functional differences in LV chamber performance, the smaller plasma volume or total blood volume might also contribute to the lower orthostatic tolerance in women. However, this possibility cannot be the entire explanation, because the difference in plasma volume or total blood volume between the genders disappeared when normalized to the body weight. In contrast, minimal stroke index was smaller in women even when normalized to body surface area, or when men and women were matched for baseline SV.

Vascular Resistance Responses During Orthostatic Stress in Women

Although HR seems to have increased appropriately for the decrease in SV (i.e., greater in women than men), the increase in vascular resistance was not different between genders. One possible interpretation of these data is that the reflex increase in vascular resistance was thus blunted in women and inadequate for the greater decrease in SV. Indeed, one recent study in astronauts suggested that the incidence of postflight orthostatic presyncope was greatest in women, and this could be ascribed to a combination of inherently low resistance and relative hypoadrenergic responses (50). Moreover, it was reported recently that the total muscle sympathetic nerve activity response to nonhypotensive head-up tilt was diminished in women despite similar increases in total peripheral resistance and decreases in CO in both genders (46).

Because we did not measure muscle sympathetic nerve activity directly in the present study, we cannot exclude the possibility that vasomotor sympathetic reserve to skeletal mus-

cle was diminished in our female subjects. However, we did measure plasma norepinephrine concentration, which increased identically in women compared with men. This finding is consistent with one recent report (16), but different from some others (7, 50). Plasma norepinephrine concentration provides an index of overall sympathetic nerve activity in normal humans under a wide variety of stressful conditions (5, 17, 22). It is increased during orthostasis, and higher elevations are associated with increased orthostatic tolerance (6, 11, 15). Also, changes in plasma norepinephrine concentration have been found to occur in direct proportion to changes in muscle sympathetic nerve activity during progressive LBNP (8).

Other investigators have demonstrated similar vasoactive responses to phenylephrine and isoproterenol between women and men (7). In keeping with this similarity in vascular reactivity and the equivalent increase in norepinephrine concentration, the increase in vascular resistance was not different between the gender groups during progressive LBNP to presyncope in the present study. Finally, when the increase in plasma norepinephrine or SVR was expressed as a function of the decrease in either SV or stroke index, we could detect no difference between men and women. This likely occurred because the smaller SV in women was countered by a greater HR, maintaining systemic flow equivalently between genders. This differential response between HR and SVR raises the provocative hypothesis that decreases in pulse amplitude (a function of SV) may preferentially influence the vagal component of the baroreflex, whereas flow in baroreceptive arteries (a function of CO) influences the sympathetic component. This hypothesis deserves further testing in additional directed research. Thus, although not dispositive, the weight of evidence suggests that the absence of any differences between genders in norepinephrine or total peripheral resistance, which is the ultimate downstream determinant of the effect of increasing

sympathetic nerve activity, argues against a physiologically meaningful impairment in vasomotor control in women.

Numerous investigations have shown that the ultimate precipitant of hypotension and syncope is sympathetic withdrawal and vasodilation (10, 24, 25, 45). Although the exact stimulus that causes this final common pathway is unknown, it has been argued that stimulation of ventricular mechanoreceptors in the setting of a small, hypercontractile heart may be one potential mechanism (26, 33, 37). Some investigators have suggested that epinephrine released from the adrenal gland may be one neuroendocrine effector of this response due to increases in both contractility and beta adrenergic-mediated vasodilation. In this study, we found that plasma epinephrine concentration was actually lower in women than in men at maximal LBNP, arguing against excessive epinephrine release as a contributing mechanism for the decreased orthostatic tolerance in women.

However, the severity of the hemodynamic stress is indicated by the hemodynamics. Women have smaller, stiffer hearts that empty faster. Therefore, in the context of a normal reflex response, they have a greater increase in HR (maintaining cardiac index) and a similar increase in vascular resistance. Our data show that in women there is simply a greater orthostatic stress. In many ways, the women behaved like the men did at greater levels of orthostatic stress. Ultimately, the individual determinant of fainting is likely to be the vasoconstrictor reserve, or the ability to respond to central hypovolemia with vasoconstriction. For example, Jardine et al. (25) reported recently that during the progressive hypotension before syncope, MAP was more closely correlated to total peripheral resistance and muscle sympathetic nerve activity than SV and CO; however, in orthostatic hypotension, progressive declines in SV and CO are the primary stimuli that ultimately lead to neurally mediated syncope.

Responses of PCWP to Orthostatic Stress in Both Genders

We found for the first time that PCWP dropped quickly at low levels of LBNP, then more slowly, and reached a plateau at high levels of LBNP to presyncope, suggesting that the heart was not totally empty before the onset of syncope. This finding is consistent with some previous echocardiographic studies, showing no further significant decrease in cardiac chamber size or volume at the time of presyncope during upright tilt (26, 33, 37). It is also consistent with the observation of Murray et al. (36) that central venous pressure decreased quickly at the beginning of a graded hypovolemia, then more slowly, and even slightly increased at syncope.

Cardiac filling pressure is consistently the first circulatory measurement reflecting hypovolemia. Exposure to even low levels of LBNP resulted in significant drops in PCWP and RAP, well before any meaningful changes in HR, BP, or CO. This can be explained by the Frank-Starling mechanism, namely, at high cardiac filling pressures, large changes in PCWP may cause only small changes in SV. The greater decrease in PCWP in women at the beginning of LBNP may be due to a greater pooling of blood to the abdominal and pelvic regions. Subsequent plateau of the PCWP curve is intriguing and unexpected. It does not appear to be due to limited venous pooling in the lower body, because calf volume increased linearly during progressive LBNP to presyncope in a protocol identical to the maximal orthostatic tolerance test in the

present study. Moreover, despite the stabilization of PCWP, SV continued to fall, and HR continued to rise during incremental LBNP, arguing for a progressively augmented peripheral pooling.

It also must be acknowledged that SV may be maintained by decreased afterload and increased contractility (both decreasing end-systolic volume), even in the face of decreasing end-diastolic volume. Unfortunately, technical difficulties limited the ability to quantify cardiac volumes accurately during high levels of LBNP. A decreased end-systolic volume would augment diastolic suction, and almost certainly is responsible for maintaining venous return in the face of very high $+G_z$ forces. Finally, the LV pressure-volume relationship may be shifted leftward at very high HRs as LV relaxation becomes incomplete between contractions. Thus, according to the time-varying elastance model of ventricular function, the presence of some wall tension during diastole may elevate the PCWP even in the face of decreasing LVEDV. We speculate that the combination of increased diastolic elastance and prominent diastolic suction are primarily responsible for the maintenance of PCWP during high-level LBNP. Other considerations including possible venoconstriction and/or tethering of the heart by the pericardium with augmented transmural pressure (i.e., decreasing pericardial pressure) may contribute to the plateau of the PCWP curve at high levels of LBNP to presyncope. However, ultimately, with progressive lower body suction, venous return will be insufficient to adequately fill the heart, and all subjects eventually faint during progressive LBNP.

In summary, the present study demonstrates that the high incidence of orthostatic intolerance in women is associated with a decreased cardiac filling during orthostatic stress. A gender-specific smaller and less "distensible" LV chamber in women may result in a larger maximal reduction in SV for a change in PCWP as a function of their Frank-Starling curves, leading to an excessive reduction in SV during orthostasis, ultimately causing orthostatic intolerance. We found no convincing evidence that the lower orthostatic tolerance in women is related to a reduced vascular resistance or hypoadrenergic response. It seems likely that human vasoconstrictor reserve is comparable in men and women, but more likely to be overwhelmed in women because of their smaller and functionally stiffer hearts. Our results suggest that differences in ventricular function and mechanics may be important mechanisms for the gender difference in orthostatic tolerance.

GRANTS

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