Lower capacitance response and capillary fluid absorption in women to defend central blood volume in response to acute hypovolemic circulatory stress

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Submitted 29 March 2008; accepted in final form 19 June 2008

Lindenberger M, Olsen H, Länne T. Lower capacitance response and capillary fluid absorption in women to defend central blood volume in response to acute hypovolemic circulatory stress. Am J Physiol Heart Circ Physiol 295: H867–H873, 2008; doi:10.1152/ajpheart.00332.2008.—Acute hemorrhage is a leading cause of death in trauma, and women are more susceptible to hypovolemic circulatory stress than men. The mechanisms underlying the susceptibility are not clear, however. The aim of the present study was to examine the compensatory mechanisms to defend central blood volume during experimental hypovolemia in women and men. Twenty-two women (23.1 ± 0.4 yr) and 16 men (23.2 ± 0.5 yr) were included. A lower body negative pressure (LBNP) of 11–44 mmHg induced experimental hypovolemic circulatory stress. The volumetric technique was used to assess the capacitance response (redistribution of peripheral venous blood to the central circulation) as well as to assess net capillary fluid transfer from tissue to blood in the arm. Plasma norepinephrine (NE) and forearm blood flow were measured before and during hypovolemia, and forearm vascular resistance (FVR) was calculated. LBNP created comparable hypovolemia in women and men. FVR increased less in women during hypovolemic stress, and no association between plasma NE and FVR was seen in women (R² = 0.01, not significant), in contrast to men (R² = 0.59, P < 0.05). Women demonstrated a good initial capacitance response, but this was not maintained with time, in contrast to men [e.g., decreased by 24 ± 4% (women) vs. 4 ± 5% (men), LBNP of 44 mmHg, P < 0.01], and net capillary fluid absorption from tissue to blood was lower in women (0.086 ± 0.007 vs. 0.115 ± 0.011 ml·100 ml⁻¹·min⁻¹, P < 0.05). In conclusion, women showed impaired vasoconstriction, reduced capacitance response with time, and reduced capillary fluid absorption during acute hypovolemic circulatory stress, indicating less efficiency to defend central blood volume than men.

gender; orthostatic tolerance; baroreceptor sensitivity

ACUTE HEMORRHAGE is a leading cause of death in trauma (2, 41). Women are more susceptible to hypovolemic circulatory stress than men (6, 13, 17, 18, 48), and clinical studies have found decreased survival in women after penetrating injury as well as burn injuries (19, 35). The mechanisms underlying the susceptibility are not entirely clear and are probably multifactorial (17).

Lower body negative pressure (LBNP) is an excellent model for acute hemorrhage and hypovolemic circulatory stress, by inducing central hypovolemia and unloading of baroreceptors (8). A decreased baroreceptor sensitivity has been proposed in women by several authors (13, 27, 42), and women seem to respond with diminished arterial vasoconstriction to the infusion of α-receptor agonists (4, 14, 26). Furthermore, a more pronounced decrease in stroke volume and cardiac output has been postulated as the main mechanism for the susceptibility to hypovolemic circulatory stress, due to smaller and functionally stiffer hearts and impeding cardiac filling (6, 17, 18) as well as lower relative circulating blood volume in women (6, 18, 49). The central hypovolemia that occurs during hypovolemic circulatory stress is compensated by displacement of blood from peripheral capacitance vessels toward the central circulation as well as by net capillary fluid absorption from tissue to blood to defend central blood volume, collectively increasing venous return to the heart (1, 8, 32, 37, 39). However, these mechanisms have not been evaluated in women.

The aim of this study was to examine cardiovascular responses and the compensatory mechanisms to maintain venous return during experimental hypovolemia in women and men. We hypothesized that women would show evidence of less pronounced defense mechanisms than men, making them more susceptible to hypovolemic circulatory stress.

METHODS

Participants

Forty-one volunteers (25 women and 16 men) were recruited to the study. Twenty-two women (23.1 ± 0.4 yr) and sixteen men (23.2 ± 0.5 yr) were included, excluding three women with missing data due to subjective and/or objective signs of presyncope. All subjects were healthy, and physical examination showed an absence of varicose veins, hypertension, diabetes, or other systemic diseases. All were non-smokers and of average physical fitness, excluding sedentary and well-trained athletes, based on an interview regarding previous and current training activities. No subjects were taking any regular medication. Women were scheduled between days 7 and 21 after the start of menstruation, not excluding oral contraceptive use (10 of 22 women studied). The type of contraceptives was not registered. Cardiovascular responses to LBNP seems to be unaffected by menstrual phase (5, 16), and, furthermore, venous compliance and capacitance do not change over the course of the menstrual cycle or with oral contraceptive use (36). Some data from the young women and men have been previously published (29, 30). Each subject gave informed consent to the experiments, which were approved by the Ethics Committee of Linköping University (Linköping, Sweden).

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**LBNP**

Experiments were performed at a stable room temperature of 23–25°C and started 1 h after a regular meal. Subjects were instructed to abstain from caffeine on the day of the investigation. The study was performed on two separate occasions, each lasting 2–3 h. In both visits, subjects were placed in the supine position with their legs enclosed in an airtight box up to the level of the iliac crest with a seal fitted hermetically around the waist. The box was connected to a vacuum source (LBNP), permitting stable negative pressure to be rapidly produced (within 5 s), continuously measured, and maintained for 8 min. Experiments were performed at LBNPs of 11, 22, and 44 mmHg, with at least 30 min between each experiment to assure return to the basal state.

**Assessment of the Hypovolemic Stimulus**

To assess the hypovolemic stimulus caused by LBNP, i.e., the pooling of blood (capacitance response) in the legs as well as net capillary fluid filtration, the change in calf volume was measured with mercury-in-Silastic strain-gauge plethysmography in all participants. Almost exclusively, venous blood is pooled since the compliance of the arterial bed is only ~3% of that of the venous bed (40). Based on previously described technique and criteria, calf venous capacitance, compliance, and net capillary filtration were calculated (29, 30). Furthermore, the time from the onset of LBNP to the development of 50% of maximal calf venous capacitance was defined (Cap_{50}). The capillary filtration coefficient (CFC; in ml·100 ml⁻¹·min⁻¹·mmHg⁻¹) in the calf was calculated as follows: \[ \text{CFC} = \frac{\frac{\text{d}V}{\Delta P \times t}}{100 \text{ ml} \cdot \text{min} \cdot \text{mmHg}} \], where \( \Delta V \) is the net capillary filtration volume during LBNP (in ml/100 ml), \( \Delta P \) is the LBNP-induced change in transmural pressure (in mmHg), and \( t \) is time during \( \Delta V \) assessment (in min).

**Capacitance Response and Net Transcapillary Fluid Absorption in the Upper Arm**

To assess venous capacitance response and transcapillary fluid absorption in response to LBNPs of 11, 22, and 44 mmHg, changes in upper arm volume were measured by air plethysmography during the first visit in all women and in 12 men (39). The air plethysmographs were cylindrical, 8 cm long, and made of transparent plastic, with openings of different sizes to fit the subject’s upper arm, and were placed at heart level. To avoid venous stasis caused by the plethysmographs, the size of the openings were slightly larger than the arm circumference. The air slits were then sealed with a soft latex compound that did not cause any additional pressure or irritation to the skin. The enclosed arm volume was calculated, and changes in tissue volume were measured with a piston recorder connected to the plethysmographs. Before each LBNP initiation, recordings ensured that the enclosed arm segment volume was stable for at least 5 min. The application of LBNP leads to a rapid decrease in arm volume, followed by a much slower but continuous decline during LBNP. At the termination of LBNP, there is a rapid increase in tissue volume, followed by a slower increase. These different phases reflect (see Fig. 1A) an initial mobilization of regional blood toward the central circulation (initial arm capacitance response); 2) net capillary absorption of extravascular fluid to intravascular space; 3) rapid recovery of regional blood after the termination of LBNP (final capacitance response); 4) total net capillary fluid absorption during LBNP; and 5) transcapillary filtration of fluid from the intravascular to extravascular space. This interpretation of tissue volume changes during acute hypovolemic circulatory stress has been validated with the aid of simultaneously measured blood and tissue volume changes in both animals (1, 37) and in humans using technetium-marked erythrocytes simultaneously with plethysmographic recordings (32). The arm capacitance response is fully developed within the first 2 min after the initiation of LBNP (32). The net transcapillary fluid absorption (in ml·100 ml⁻¹·min⁻¹) was measured as the difference in arm volume before LBNP and the volume 1 min after the termination of LBNP (Fig. 1A). In many registrations, there was, however, a gradual reduction of the initial capacitance with time during LBNP (Fig. 1B). To be able to define the initial capacitance and transcapillary fluid absorption in these curves, the following assumptions were applied in all registrations. First, the maximal arm volume reduction during the first 2 min of LBNP was identified. The total net capillary fluid absorption (4) (Fig. 1) was then added, defining the total volume reduction at the termination of LBNP (X; Fig. 1). From X, a tangent was drawn adjoining the lowest part of the volume curve during the initial 2 min of LBNP, defining the initial capacitance response (Fig. 1B). The final capacitance response at the termination of LBNP was defined as described above (3) (Fig. 1). The rate of development of the

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Fig. 1. A: original tracing illustrating tissue volume changes in the upper arm of a man during 8 min of lower body negative pressure (LBNP) of 44 mmHg. The initial rapid volume decrease reflects mobilization of regional blood from the peripheral to central circulation [initial capacitance response (1)], whereas the much slower but continuous decline reflects net transcapillary fluid absorption (2). After the cessation of LBNP, there was a rapid return of regional blood volume [final capacitance response (3)], with the total volume of absorbed fluid after LBNP termination as shown (4) and followed by a gradual, slow net capillary refiltration of fluid (5). B: original tracing illustrating tissue volume changes in the upper arm during 8 min of LBNP of 44 mmHg in a woman. After the fast initial capacitance response, there was a gradual reduction of the capacitance response during LBNP, resulting in a visibly decreased final capacitance response at the termination of LBNP. See the text for further details.
Cardiovascular Response

Blood pressure and heart rate were measured repeatedly before, during, and after LBNP noninvasively by oscillometric techniques (Dinamap Pro 200, Critikon). During the second visit, forearm blood flow (FFB) was measured in the right forearm in all women and in 12 men by standard venous occlusion strain-gauge plethysmography (Hokanson EC-6, Hokanson, Bellevue, WA), with the forearm at heart level and the strain-gauge at the maximal forearm circumference, and hand blood flow was occluded at least 1 min before each measurement. The FFB was measured repeatedly at baseline and 0.5, 1, 3, 6, and 8 min after the initiation of LBNP. Forearm vascular resistance (FVR) was calculated as mean arterial blood pressure (MAP) divided by FBF.

Plasma Norepinephrine

Plasma levels of norepinephrine (NE) were measured at rest and after 4 min of LBNP of 44 mmHg in all women and in 12 men, since by this time the increase in plasma NE has almost completely developed (12). Blood samples were kept on ice, centrifuged within 20 min, stored in a −70°C freezer, and later analyzed with HPLC techniques. Unfortunately, 5 samples were destroyed in the freezing process, resulting in plasma NE data in 19 women and 10 men.

Statistical Evaluation

All data are given with reference to soft tissue weight, excluding bone [10% in the calf and 13% in the forearm (9, 21)]. Values are expressed as mean ± SE. The area under the curve (AUC) for FVR was calculated from the initiation to termination of LBNP. The significance of differences between the groups was tested by an unpaired Student’s t-test. A paired Student’s t-test was used to test differences within each group. Repeated-measures ANOVA was used to test whether the arm measurements responded to an LBNP increase unpaired Student’s t-test was used to test whether the level or change in plasma NE and FVR could be explained by the level or change in plasma epinephrine; NS, not significant. FBF, forearm blood flow; FVR, forearm vascular resistance; NE, norepinephrine; NS, not significant.

Net capillary filtration. Total net capillary filtration during LBNPs of 11, 22, and 44 mmHg was 32 ± 0.02, 0.58 ± 0.02, and 1.21 ± 0.06 ml/100 ml in women and 0.24 ± 0.02, 0.48 ± 0.04, and 1.11 ± 0.06 ml/100 ml in men, with women having higher capillary filtration at LBNPs of 11 and 22 mmHg and overall (P < 0.05). CFC was unaffected by the LBNP level in both sexes and was 0.0043 ± 0.0002 ml-1 min-1·mmHg-1 in women and 0.0036 ± 0.0002 ml-1 min-1·mmHg-1, being greater in women (P = 0.02).

Total calf volume increase. The total calf volume increase (i.e., capacitance response + total filtration) during LBNPs of 11, 22, and 44 mmHg was 1.00 ± 0.05, 1.96 ± 0.08, and 3.47 ± 0.11 ml/100 ml in women and 1.16 ± 0.09, 2.22 ± 0.14, and 3.77 ± 0.20 ml/100 ml in men, being equivalent in women and men at all LBNP levels.

Cardiovascular Responses

Table 2 shows maximal cardiovascular responses, in relation to resting values, in women and men evoked by 8 min of LBNP of 44 mmHg, with women having a smaller increase in FVR and a concomitant decrease in FBF than men (P < 0.05) and a higher increase in plasma NE in (in percent change and in absolute values, P < 0.05). No sex differences were detected in heart rate or any blood pressure parameters.

Figure 2 shows the change in FVR in women and men during LBNP of 44 mmHg. FVR peaked 30 s after the initiation of LBNP in both groups, with women having a lower increase in FVR during the first 3 min of LBNP (P < 0.05) as well as overall (AUC, P < 0.01).

COMPENSATORY MECHANISMS TO HYPOVOLEMIC STRESS IN WOMEN

Table 1. Demographic resting values in young women and men

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>No. of subjects</td>
<td>22</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>23.1 ±0.4</td>
<td>23.2±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169±1</td>
<td>181±1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62±2</td>
<td>72±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.7±0.4</td>
<td>21.8±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>60±2</td>
<td>56±2</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>106±1</td>
<td>116±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>63±1</td>
<td>60±1</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>77±1</td>
<td>78±1</td>
<td>NS</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>43±2</td>
<td>56±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FBF, ml·100 ml ·1·min⁻¹</td>
<td>2.2±0.2</td>
<td>3.0±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FVR, FVR units</td>
<td>37±3</td>
<td>28±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Plasma NE, pmol/l</td>
<td>1.2±0.1</td>
<td>1.6±0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; PP, pulse pressure; FBF, forearm blood flow; FVR, forearm vascular resistance; NE, norepinephrine; NS, not significant.
Peripheral Effector Responses

Figure 3A shows the relation between plasma NE and FVR in women and men at rest. In women, no significant relation was found ($R^2 = 0.03$, NS), but in men, a positive relation was found ($R^2 = 0.67$, $P < 0.05$). Figure 3B shows the relation between the increase in plasma NE and FVR in women and men during LBNP. No significant relation was found in women ($R^2 = 0.01$, NS), but in men, a positive relation was found ($R^2 = 0.59$, $P < 0.05$). Furthermore, men had a steeper slope of the regression line than women during hypovolemic stress ($P = 0.002$), i.e., a similar increase in plasma NE in both sexes, which generates a much greater increase in FVR in men than in women.

Arm Volumetric Responses

Figure 4A shows initial arm capacitance responses during LBNP in women and men. Initial capacitance responses during LBNPs of 11, 22, and 44 mmHg were $0.78 \pm 0.04$, $1.08 \pm 0.07$, and $1.50 \pm 0.09$ ml/100 ml in women and $0.55 \pm 0.03$, $0.92 \pm 0.06$, and $1.29 \pm 0.10$ ml/100 ml in men, with higher initial capacitance responses in women during LBNP of 11 mmHg ($P < 0.001$) and overall ($P < 0.05$). Both sexes increased their initial capacitance response with increasing LBNP levels of 11, 22, and 44 mmHg ($P < 0.0001$). Women had a faster and greater increase in capacitance response during the first 30 s of LBNP of 44 mmHg (both in absolute values and in percent, $P = 0.01$). Furthermore, Fig. 4 shows the reduction in capacitance responses during 8 min of LBNP (i.e., initial capacitance response minus final capacitance response) in absolute values ($B$) and percentages ($C$). Women had a greater reduction in capacitance responses at all three LBNP levels ($P < 0.01$).

Figure 5 shows the net capillary fluid absorption during LBNP in women and men. The fluid absorption during LBNPs of 11, 22, and 44 mmHg was $0.048 \pm 0.006$, $0.066 \pm 0.007$, and $0.086 \pm 0.007$ ml/100 ml$^{-1}$min$^{-1}$ in women, with corresponding values of $0.043 \pm 0.005$, $0.082 \pm 0.004$, and $0.115 \pm 0.011$ ml/100 ml$^{-1}$min$^{-1}$ in men, with women having lower absorption at LBNP of 44 mmHg as well as overall ($P < 0.05$). The capillary fluid absorption increased with increasing LBNP in both groups ($P < 0.0001$), but men responded with a more pronounced augmentation in net capillary absorption with increasing hypovolemia than women ($P < 0.05$).

DISCUSSION

The main findings in this study were as follows. First, the calf capacitance response was lower and net calf capillary filtration higher (due to higher CFC) in women than in men, leading to a similar hypovolemic load during LBNP. Second, FVR increased less in women during hypovolemic circulatory stress, and no relation between plasma NE and FVR was seen, in contrast to the strong relation observed in men. Finally, mobilization of capacitance blood with time as well as net capillary fluid absorption from peripheral tissues were lower in women than in men, indicating decreased defense of central blood volume in women in response to hypovolemic circulatory stress.

A leading cause of death in civilian trauma is acute hemorrhage (2, 41). Young women are more susceptible to hypovolemic circulatory stress than young men (6, 13, 17, 18, 48). The mechanisms underlying this susceptibility in women are not clear, however, and are probably multifactorial (17). LBNP is an excellent model to simulate acute hemorrhage and hypovolemic circulatory stress in humans, by unloading the baroreceptors due to central hypovolemia (8). When evaluating sex differences in cardiovascular responses to LBNP, it is, however, of importance to consider the hypovolemic stimulus, since sex differences have been seen in both calf capacitance responses (30, 36, 38) and calf net capillary fluid filtration (30). Our results confirm a lower calf venous capacitance and venous compliance in women as well as a higher net capillary fluid filtration, due to higher CFC. Although calf venous capacitance and compliance do not seem to be affected by sex hormones (36), the higher CFC may be a result of the increased estrogen levels and the effect of estrogen on the microcirculation (30, 44, 47). The total hypovolemic load was similar between sexes (30, 49). This finding is supported by Franke et al. (13), who measured the effect of LBNP on central venous pressure and thoracic impedance and found similar levels of central hypovolemic circulatory stress in women and men. Not only the applied hypovolemic stimulus but also the speed by

<table>
<thead>
<tr>
<th>HR</th>
<th>SBP</th>
<th>DBP</th>
<th>MAP</th>
<th>PP</th>
<th>FBF</th>
<th>FVR</th>
<th>Plasma NE</th>
</tr>
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<tbody>
<tr>
<td>Women</td>
<td>137±4</td>
<td>94±1</td>
<td>104±1</td>
<td>100±1</td>
<td>77±3</td>
<td>62±3*</td>
<td>180±11*</td>
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<tr>
<td>Men</td>
<td>135±4</td>
<td>94±1</td>
<td>109±2</td>
<td>102±1</td>
<td>74±3</td>
<td>50±7</td>
<td>255±39</td>
</tr>
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</table>

Percentage of resting values are means ± SE. *Sex differences ($P < 0.05$).
which it was initiated seems to be of importance for the cardiovascular response, since a more rapidly induced hypovolemic stimulus elicits a greater circulatory response (28). No sex differences in Cap50 were found, however. Thus, the volemic stimulus elicits a greater circulatory response (28). No cardiovascular response, since a more rapidly induced hypovolemic load in women but rather in differences in the autonomic regulation of the cardiovascular system (13, 25).

Plasma NE is a good marker of the overall sympathetic response and correlates well with muscle sympathetic nerve activity (MSNA) as well as peripheral resistance (7, 11, 20, 23). At rest, plasma NE was equal in women and men (Table 1). As expected, an association between plasma NE and FVR was seen in men at rest. However, no such relation was found in women, in line with findings by Hogarth et al. (24), who reported a positive relation between MSNA and calf FVR at rest in men but not in women (Fig. 3A). The increase in plasma NE was greater in women than in men during LBNP, whereas FVR increased less in women (Fig. 2) (15). Thus, plasma NE initiated a less potent vasoconstriction in women, and the lack of association between plasma NE and FVR in women was also maintained during LBNP (Fig. 3B). Sudhir et al. (45) demonstrated that estrogen may attenuate forearm vasoconstrictor responses to an infusion of NE in women. Freedman et al. (14) detected a less pronounced increase in arterial vasoconstriction to an infusion of α-receptor agonists in women compared with men and suggested a decreased density or sensitivity of peripheral vascular adrenergic receptors in women (4, 14, 26). Kneale et al. (26) extended these observations, and, in addition to the increased vasoconstriction found in men, they detected an increased β2-receptor vasodilatation in women to an infusion of β-receptor agonists. Interestingly, when propranolol (a β-receptor antagonist) was confused with NE, the sex difference in vasoconstriction disappeared. Thus, plasma NE in women might have relatively higher affinity to β2- than α1-receptors, impeding vasoconstriction (26). This could explain the decreased vasoconstriction seen in women despite their increased plasma NE response (Fig. 2 and Table 2). Decreased baroreflex sensitivity in women has been suggested by several authors using both baroreceptor unloading and nonunloading techniques (13, 27, 42), which also potentially affect vasoconstrictor responses.

During LBNP of 11 mmHg, a level generally ascribed to unload cardiopulmonary receptors (33), although challenged by Taylor et al. (46), FVR increased in women but not in men 30 s after the initiation of LBNP (data not shown). Concomitantly, the initial arm capacitance response was greater at LBNP of 11 mmHg in women (Fig. 4A). With increasing hypovolemic stimuli (increasing unloading of arterial baroreceptors), the initial arm capacitance responses in women and men increased in a similar fashion (Fig. 4A). These findings indicate a higher sensitivity of cardiopulmonary receptors in women, in accordance with Hinojosa-Laborde et al. (22). FVR peaked 30 s after the initiation of LBNP to decline to a lower, fairly stable level throughout LBNP in both women and men, being significantly lower in women (Fig. 2), and tended to return toward resting levels, especially in women. Furthermore, women did not maintain their arm capacitance responses over time to the same extent as men (Fig. 4, B and C). These findings might explain the sex difference in changes in blood pressure after the first minute of prolonged quiet standing, where men tended to increase their systolic blood pressures, whereas women did not (31). Different contractile responses to neurally released NE have been shown in vessels of various
sizes. In small muscular arteries and arterioles, the distance between sympathetic nerve endings and smooth muscle cells is short, and responses to NE are fast and initially great but not maintained over time. In larger arteries, the distance between synapses and smooth muscle cells is greater, and since NE relies both on diffusion and neuronal reuptake within the vessel wall, this results in a slower and smaller response but is maintained over time (3). It may be hypothesized that women primarily rely to a larger extent on arterial vasoconstriction of smaller arteries, i.e., fast but not maintained, whereas men rely on vasoconstriction in larger arteries with slower but maintained responses over time (3, 31). The more pronounced return in FBF during LBNP and the initially faster but less maintained arm capacitance response as well as decreased net capillary fluid absorption in women support this theory (Figs. 4, B and C, and 5). An effective net capillary fluid absorption is dependent on both high hydrodynamic conductivity as well as capillary pressure reduction with increased transmural pressure gradients over microvessel walls. Despite a higher CFC, capillary fluid absorption was lower in women than in men during hypovolemic circulatory stress, which may seem contradictory. However, the effect of the lesser $\alpha_1$-mediated sympathetic vasoconstriction seen in women with a concomitant smaller reduction in capillary pressure (34) might affect the capillary fluid absorption to a higher extent (4, 14, 26). The less pronounced increase in net capillary fluid absorption with increasing hypovolemia in women further supports this theory (Fig. 5).

The earlier onset of hypotension in women during circulatory stress has been associated with a more prominent decrease in stroke volume and cardiac output, being more evident during hypovolemic conditions (6, 10, 17, 18). Hypothesized mechanisms for the faster decrease in stroke volume have been smaller and less distensible hearts in women (17, 18). We suggest an alternative explanation: the functional importance of the capacitance response and net absorption during hypovolemic stress might at first glance seem unimpressive, but when taking into consideration the total mass of skeletal muscle and skin in the human body (~40 kg in a 70-kg adult man (43)], a rough calculation gives the following result. The combined effect of the capacitance response and transcapillary fluid absorption during the limited period of 8 min of hypovolemic circulatory stress, corresponding to LBNP of 44 mmHg, adds another 900 ml to the effective circulating blood volume. A well-maintained capacitance response and net capillary fluid absorption seem to constitute very important compensatory responses for the restitution of plasma volume during acute hemorrhage and hypovolemia (28). The inability for women compared with men to defend central blood volume with time might thus be due to the reduced capacitance response with time and decreased net capillary absorption, leading to a decrease in venous return to the heart and thus a more prominent reduction in stroke volume.

**Limitations of the Study**

First, women were scheduled between days 7 and 21 after the start of menstruation, and estrogen levels were not measured. However, cardiovascular responses to LBNP seem to be unaffected by menstrual phase (5, 16). Furthermore, venous compliance and capacitance do not change over the course of the menstrual cycle (36). Second, 10 of the women were using oral contraceptives, and the type was not registered. Oral contraceptives can influence the cardiovascular system in many ways (e.g., Refs. 4 and 44), potentially influencing our findings. However, calf venous compliance and capacitance seem to be unaffected by oral contraceptive use (36). Furthermore, no significant differences were found in calf venous compliance, capacitance, CFC, or in any of the cardiovascular responses measured (arm capacitance response, net capillary fluid absorption, blood pressure, heart rate, FBF, or FVR at rest or during LBNP) when normally menstruating women ($n = 12$) were compared women using oral contraceptives ($n = 10$). Our study design cannot differentiate between the effect of estrogen and sex, and the presented data are likely to represent a general response to hypovolemic circulatory stress in women compared with men.

**Conclusions**

Calf venous compliance as well as calf capacitance responses were lower and net calf capillary filtration was greater (due to higher CFC) in women than in men, leading to similar hypovolemic load during LBNP. FVR increased less in women during hypovolemic circulatory stress. Furthermore, the expected relation between plasma NE and FVR was absent in women both at rest and during hypovolemic circulatory stress, in contrast to the strong associations found in men. Despite an initially good mobilization of capacitance blood from peripheral tissues to the central circulation in response to hypovolemic circulatory stress, the defense of central blood volume in women was not maintained with time, and net capillary fluid absorption from tissue to blood was lower in women than in men, making women more susceptible to acute hypovolemic circulatory stress and hemorrhage.

**GRANTS**

This work was supported by grants from the Medical Faculty, Linköping University; Futurum—the Academy of Health Care, Jönköping County Council; Medical Research Council Grant 12661; and the Heart and Lung Foundation.
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