Decreased capillary filtration but maintained venous compliance in the lower limb of aging women

Marcus Lindenberger1,2 and Toste Lånne1
1Division of Physiology, Department of Medicine and Care, Linköping University, Linköping, Sweden; and 2Division of Cardiology, Department of Medicine, Ryhov County Hospital, Jönköping, Sweden

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Lindenberger M, Lånne T. Decreased capillary filtration but maintained venous compliance in the lower limb of aging women. Am J Physiol Heart Circ Physiol 293: H3568–H3574, 2007. First published September 28, 2007; doi:10.1152/ajpheart.00725.2007.—There are sex-related differences in venous compliance and capillary filtration in the lower limbs, which to some extent can explain the susceptibility to orthostatic intolerance in young women. With age, venous compliance and capacitance are reduced in men. This study was designed to evaluate age-related changes in venous compliance and capillary filtration in the lower limbs of healthy women. Included in this study were 22 young and 12 elderly women (23.1 ± 0.4 and 66.4 ± 1.4 yr). Lower body negative pressure (LBNP) of 11, 22, and 44 mmHg created defined transmural pressure gradients in the lower limbs. A plethysmographic technique was used on the calf to assess venous capacitance and net capillary filtration. Venous compliance was calculated with the aid of a quadratic regression equation. No age-related differences in venous compliance and capacitance were found. Net capillary filtration and capillary filtration coefficient (CFC) were lower in elderly women at a LBNP of 11 and 22 mmHg (0.0032 vs. 0.0044 and 0.0030 vs. 0.0041 ml·100 ml−1·min−1·mmHg−1, P < 0.001). At higher transmural pressure (LBNP, 44 mmHg), CFC increased by ∼1/3 (0.010 ml·100 ml−1·min−1·mmHg−1) in the elderly (P < 0.001) but remained unchanged in the young women. In conclusion, no age-related decrease in venous compliance and capacitance was seen in women. However, a decreased CFC was found with age, implying reduced capillary function. Increasing transmural pressure increased CFC in the elderly women, indicating an increased capillary susceptibility to transmural pressure load in dependent regions. These findings differ from earlier studies on age-related effects in men, indicating sex-specific vascular aging both in the venous section and microcirculation.

Capillary filtration coefficient; lower body negative pressure; age

A transition from the supine to standing posture leads to a progressive pooling of blood in the compliant veins in the lower part of the body, which produces an immediate circulatory challenge due to the concomitant decrease in thoracic blood volume (5, 6, 39). Subjects with increased limb venous compliance have been shown to have greater orthostatic intolerance, probably due to an increased venous capacitance (24, 36, 46), although this relationship has recently been challenged by Hernandez and Franke (18). Venous compliance in the lower limbs decreases with age in men (33, 38, 39, 49), but there is no reason to believe that venous compliance and capacitance are similar in men and women, since a sex difference has been established in young adults (26, 30, 34). Furthermore, age-related changes might be sex specific, in accordance with age-related changes of arteries, with women having a slower decrease in arterial compliance with age compared with men, an effect probably attributed to estrogen (9, 48). Estrogen has been shown to affect cellular transcription of elastin and collagen, and estrogen-receptors are known to exist in vascular smooth muscle cells (21, 22, 32).

There is a marked capillary fluid filtration in the lower limb during quiet standing or lower body negative pressure (LBNP), increasing the hypovolemic stimulus over time independently from venous compliance and capacitance, and its hypovolemic importance is indicated by the increased fluid filtration in lower limbs of subjects with postural tachycardia syndrome (25, 26, 46). We recently described an increased capillary fluid filtration and capillary filtration coefficient (CFC) in the calf of young women compared with men, possibly caused by higher levels of estrogen in women, since estrogen enhances capillary filtration (26, 45, 47). Despite the marked drop in estrogen levels during menopause, the effects of aging on capillary fluid filtration and CFC have not been examined in women.

The aim of the present study was to study age-related changes in venous compliance, capacitance, and capillary filtration in the calf of healthy women, in response to defined transmural pressure gradients. We hypothesized that the effect of aging on venous compliance and capacitance would be nonsignificant and, furthermore, that capillary fluid filtration would decrease with age in women.

METHODS

A total of 34 volunteers, 12 elderly and 22 young women, were included in the study, excluding a total of four subjects (1 elderly and 3 young) who experienced subjective or objective signs of vagal reactions at the highest LBNP level. All subjects were healthy with no history of cardiovascular disease, and a physical examination showed the absence of deep or superficial varicose veins, hypertension, diabetes, or any other serious systemic disease. All were nonsmokers, and based on an interview regarding earlier and current training activities, all selected volunteers were of average physical fitness, excluding sedentary as well as well-trained athletes. No subjects were taking any regular medication. The young women were scheduled in the middle 2 wk of their menstrual cycle, not excluding oral contraceptive use (10 subjects). Venous compliance does not seem to change over the course of the menstrual cycle or by oral contraceptive use (30). Data from 12 of the young women have been previously published (26). Each subject gave informed consent to the experiments approved by the Ethics Committee of Linköping University, Sweden.

The experiments were performed at a stable room temperature of 23–25°C and started 1 h after a regular meal. The subjects were instructed to abstain from coffee, tea, or caffeine on the day of the experiment, and were instructed to abstain from coffee, tea, or caffeine on the day of the experiment.
investigation. Throughout the experiments, continuous efforts were made to maintain a relaxed and quiet atmosphere. The study was performed on two separate occasions, each lasting 2 to 3 h since the experiments were time consuming.

The subjects were placed in the supine position with the 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). The pressure in the LBPN chamber was continuously measured by a manometer (DT-XX disposable transducer, Viggo Spectramed, Helsingborg, Sweden) and held constant by a rheostat. During LBPN, 80% of the negative pressure is transmitted to the underlying muscle tissue of the leg irrespective of muscle depth, time, and magnitude, leading to a defined increase in transmural pressure over the vessel wall, with concomitant vessel dilatation and blood pooling (38). Since the compliance of the arterial bed is only \( \approx 3\% \) of that of the venous bed, almost exclusively venous blood is pooled (41). The advantages using negative pressure instead of venous occlusion technique have previously been discussed (26).

To assess the hypovolemic stimulus caused by LBPN, i.e., the pooling of blood (capacitance response) in the legs and net capillary fluid filtration, the change in calf volume was measured with mercury-in-silastic strain-gauge plethysmography. This method is designed for measuring volume changes (in ml/100 ml) of a limb by measuring the circumference. The strain gauge was applied at the maximal circumference of the right calf. The basal venous pressure was not measured, but care was taken to place the calf 5 cm below the heart level in all subjects, and to avoid any confounding external pressure, the lowest part of the calf was at least 2 cm above the floor of the LBPN chamber. Furthermore, the subjects rested in the supine position for at least 30 min before the LBPN stimulus to ensure stable calf volume and arterial inflow. LBPN was then rapidly instituted and maintained for 8 min. The experiments were performed at LBPN of 11, 22, and 44 mmHg, in ascending order, with at least 30 min in between each experiment to ensure that the basal state was restored. The pressure interval used was defined according to the following considerations: volume registrations from the calf at LBPN pressures lower than 10 mmHg may be somewhat unreliable. We therefore used 11 mmHg in the interval used was defined according to the following considerations: volume registrations from the calf at LBPN pressures lower than 10 mmHg may be somewhat unreliable. We therefore used 11 mmHg in

The CFC (in ml \( \cdot 100 \text{ ml}^{-1} \cdot \text{mmHg}^{-1} \)) was measured by a modified version of the technique developed by Lanne and colleagues (26, 38) and has been previously described. In short, each calf venous capacitance response (i.e., total calf volume increase excluding capillary fluid filtration) was related to the increase in transmural pressure (80% of the applied negative pressure; Fig. 2A). The resulting volume-pressure curve was nonlinear with larger volume changes (greater compliance) at lower transmural pressures as described by a quadratic regression equation:

\[
\Delta \text{calf volume} = \beta_0 + \beta_1 \times (\text{transmural pressure}) + \beta_2 \times (\text{transmural pressure})^2
\]

where \( \beta_0 \) is the \( y \)-intercept and \( \beta_1 \) and \( \beta_2 \) are characteristics of the slope of the volume-pressure curve. Since venous compliance is dependent on pressure, no single value can characterize the slope of this relation. To simplify data presentation, the first derivative of the volume-pressure curve (\( C = \beta_1 + 2 \times \beta_2 \times \text{transmural pressure} \)) was calculated, creating a linear compliance-pressure curve (Fig. 2B). The slope of the curve equals the derivative of the compliance-pressure curve (slope = \( 2 \times \beta_2 \)) and was used as well as the two components \( \beta_1 \) and \( \beta_2 \) to determine potential differences in calf venous compliance. The impact of capillary fluid filtration when calculating compliance was studied with the use of the calf volume increase caused by total calf volume increase (i.e., not excluding capillary fluid filtration), which was then compared with the standard compliance calculations using venous capacitance (i.e., total calf volume increase excluding capillary fluid filtration).

The CFC (in ml \( \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \)) in the calf was calculated as \( \Delta \text{CFC} = \Delta \text{V} / (\Delta \text{P} \cdot \beta_0) \), where \( \Delta \text{V} \) denotes capillary filtration volume during LBPN (minutes 3–8 after institution of LBPN; in ml/100 ml), \( \Delta \text{P} \) denotes the LBPN-induced change in transmural pressure (in mmHg), and \( t \) (in min) denotes time during \( \Delta \text{V} \) assessment.

Forearm blood flow (FBF) was measured in the right forearm by standard venous occlusion mercury-in-silicone elastomer strain-gauge plethysmography (Hokanson EC-6, D. E. Hokanson, Bellevue, WA). With the person in the supine position with the lower part of the body enclosed in the vacuum chamber, the forearm was placed at heart level
and the strain gauge was placed at the maximal forearm circumference. Occlusion of hand blood flow was accomplished by a wrist cuff inflated 100 mmHg above systolic blood pressure at least 1 min before measuring the FBF. The FBF was measured repeatedly at baseline and 8 min after the institution of the LBNP. Simultaneously, blood pressure was measured noninvasively in the contralateral arm by oscillometric technique (Dinamap Pro 200, Critikon). Forearm vascular conductance (FVC) was calculated as FBF divided by mean arterial blood pressure.

During the second visit, a catheter was inserted in the antecubital vein and blood was drawn for analysis of plasma levels of norepinephrine (P-NE). P-NE was measured in 10 elderly and 18 young women at rest before LBNP and after 4 min of LBNP of 44 mmHg, since after this time the increase in P-NE is almost completely developed (10). The blood sample was kept on ice, centrifuged within 20 min, stored in a −70°C freezer, and later analyzed with HPLC/MS technique.

All data are given with reference to soft tissue weight excluding bone, with bone taken as 10% in the calf and 13% in the forearm (7, 15). Values are expressed as means ± SE. The significance of difference between the two groups was tested by unpaired Student’s t-test. Paired Student’s t-test was used to test the difference within each group (the effect of transmural pressure on venous compliance, CFC, and the effect of filtration on the compliance calculations). ANOVA was used to test whether CFC and transmural pressure was positively correlated within each group, and if a positive correlation was found, Tukey simultaneous tests was used to assess differences in CFC between the three pressure levels. When we calculated compliance, each subject’s own volume-pressure curve was adjusted to a regression equation, and \( \beta_0, \beta_1, \) and \( \beta_2 \) were stored individually. Each parameter was then compared between the groups with unpaired Student’s t-test. Coefficient of variation (in %) was calculated for filtration and capacitance response at different measurements. Statistical significance was set to \( P < 0.05 \).

RESULTS

Table 1 shows the demographic values at rest in 12 elderly and 22 young women included in the study. There were no differences in height or body weight, but the elderly women had a slightly higher body mass index (BMI). Furthermore, the elderly women had higher blood pressure and P-NE but lower FVC.

Figure 2A shows the volume-pressure curve created from the increase in venous capacitance response with increasing LBNP in the calf of elderly and young women. Venous capacitance during LBNP of 11, 22, and 44 mmHg (calculated transmural pressure increase from 9 to 36 mmHg) was 0.67 ± 0.07, 1.29 ± 0.10, and 2.14 ± 0.11 ml/100 ml in elderly and 0.68 ± 0.04, 1.35 ± 0.07, and 2.26 ± 0.09 ml/100 ml in young women, without significant differences. Figure 2B shows the corresponding venous compliance curves. It is clear that venous compliance is dependent on transmural pressure (higher at low transmural pressure), with a reduction in compliance in elderly from 0.77 to 0.032 ml/100 ml⁻¹·mmHg⁻¹ at transmural pressure of 9 to 36 mmHg, with a corresponding reduction of 0.083 to 0.034 ml/100 ml⁻¹·mmHg⁻¹ in young women (\( P < 0.001 \) in both groups). The parameters of the quadratic regression equation were \(-0.088 \pm 0.086 (\beta_0), 0.092 \pm 0.012 (\beta_1), \) and \(-0.00083 \pm 0.00025 (\beta_2) \) in the elderly and \(-0.142 \pm 0.048 (\beta_0), 0.100 \pm 0.007 (\beta_1), \) and \(-0.00092 \pm 0.00014 (\beta_2) \) in young women. No differences in \( \beta_0, \) or any calf venous compliance parameters, between elderly and young women were seen (\( \beta_1, P = 0.55; \) and \( \beta_2 \) and slope, \( P = 0.75 \)).

The time to 50% of the venous capacitance response in the calf to be developed (Cap50) during LBNP of 11, 22, and 44 mmHg was 11 ± 1, 20 ± 3, and 26 ± 4 s in elderly and 10 ± 1, 19 ± 1, and 26 ± 2 s in young women, with increasing time to Cap50 during increasing LBNP levels in both groups (\( P < 0.001 \)) but with no differences between elderly and young women.

Figure 3 shows the capillary fluid filtration in the calf during 8 min LBNP in elderly and young women. The capillary filtration coefficient (CFC) between the three pressure levels. When we calculated compliance, each subject’s own volume-pressure curve was adjusted to a regression equation, and \( \beta_0, \beta_1, \) and \( \beta_2 \) were stored individually. Each parameter was then compared between the groups with unpaired Student’s t-test. Coefficient of variation (in %) was calculated for filtration and capacitance response at different measurements. Statistical significance was set to \( P < 0.05 \).

Table 1. Demographic resting values in young and elderly women

<table>
<thead>
<tr>
<th></th>
<th>Young (n=22)</th>
<th>Elderly (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>23.1±0.4</td>
<td>66.4±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169±1</td>
<td>166±1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62±2</td>
<td>64±2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.7±0.4</td>
<td>23.4±0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>60±2</td>
<td>63±2</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>106±1</td>
<td>138±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>63±1</td>
<td>82±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>77±1</td>
<td>101±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>43±2</td>
<td>57±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBF, ml/100 ml⁻¹·min⁻¹</td>
<td>2.2±0.2</td>
<td>1.9±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FVC, units</td>
<td>0.027±0.002</td>
<td>0.018±0.003</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P-NE, pmol/l</td>
<td>1.2±0.1</td>
<td>2.2±0.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of women; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; FBF, forearm blood flow; FVC, forearm vascular conductance; P-NE, plasma norepinephrine; NS, not significant.
affected, both in elderly (calf volume increase, the compliance calculations were applied transmural pressure in the young women. In both groups, FBF and FVC decreased with increasing LBNP levels (P < 0.001). The decrease in P-NE during LBNP of 44 mmHg was 89 ± 20% in elderly and 89 ± 16% in young women, with no difference seen with age.

Coefficient of variation for venous capacitance and capillary filtration was 8.4% and 9.6%, respectively.

When the young women with (n = 10) and without (n = 12) oral contraceptive use were compared regarding venous compliance, capacitance, and CFC, no significant differences were found.

DISCUSSION

The main findings in this study were as follows. First, calf venous compliance and capacitance did not change with age in healthy women. Second, interstitial fluid accumulation due to filtration during LBNP of 11, 22, and 44 mmHg was 0.028 ± 0.002, 0.053 ± 0.003, and 0.146 ± 0.009 ml·100 ml⁻¹·min⁻¹ in elderly and 0.039 ± 0.002, 0.073 ± 0.003, and 0.151 ± 0.008 ml·100 ml⁻¹·min⁻¹ in young women, with elderly having reduced capillary filtration at LBNP of 11 and 22 mmHg (each P < 0.001).

Figure 4A shows the CFC in the calf during LBNP in elderly and young women. CFC during LBNP of 11, 22, and 44 mmHg (calculated transmural pressure increase from 9 to 36 mmHg) was 0.0032 ± 0.0002, 0.0030 ± 0.0002, and 0.0041 ± 0.0002 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹ in elderly and 0.0044 ± 0.0002, 0.0041 ± 0.0002, and 0.0042 ± 0.0002 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹ in young women, with elderly having reduced CFC compared with young women at transmural pressure of 9 and 18 mmHg (each P < 0.001) but similar CFC at 36 mmHg (P = 0.93). Figure 4B shows the corresponding changes in CFC with increasing LBNP (% of CFC value at transmural pressure of 9 mmHg). CFC was pressure dependent in the elderly women (P < 0.001) and was 0.009 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹ higher at LBNP of 44 mmHg compared with LBNP of 11 mmHg (P = 0.008) and 0.011 ml·100 ml⁻¹·min⁻¹·mmHg⁻¹ higher at LBNP of 44 mmHg than at LBNP of 22 mmHg (P = 0.002). CFC was unaffected by applied transmural pressure in the young women.

If net capillary filtration was not excluded from the total calf volume increase, the compliance calculations were affected, both in elderly (β₁, 0.092 ± 0.012 vs. 0.094 ± 0.014, not significant; and β₂, -0.00083 ± 0.00025 vs. -0.00011 ± 0.00029, P < 0.001) and in the young women (β₁, 0.100 ± 0.007 vs. 0.124 ± 0.010, P < 0.01; and β₂, -0.00092 ± 0.00014 vs. -0.00072 ± 0.00020, P = 0.07), with the first value being with filtration excluded, followed by calculated compliance when not excluding capillary filtration.

The decrease in FBF and FVC was greatest 30 s after the institution of LBNP and was then increased toward a reasonably constant level after 3 min. Table 2 shows the mean decrease in FBF and FVC (% of baseline value) 3–8 min after institution of LBNP of 11, 22, and 44 mmHg in elderly and young women. In both groups, FBF and FVC decreased with increasing LBNP levels (P < 0.05). However, no differences were seen between elderly and young women. P-NE increased in both groups during LBNP (P < 0.001). The increase in P-NE during LBNP of 44 mmHg was 89 ± 20% in elderly and 89 ± 16% in young women, with no difference seen with age.

Coefficient of variation for venous capacitance and capillary filtration was 8.4% and 9.6%, respectively.

When the young women with (n = 10) and without (n = 12) oral contraceptive use were compared regarding venous compliance, capacitance, and CFC, no significant differences were found.

DISCUSSION

The main findings in this study were as follows. First, calf venous compliance and capacitance did not change with age in healthy women. Second, interstitial fluid accumulation due to
capillary fluid filtration was reduced in elderly women, probably
due to lower CFC than in the young. This was, however,
evident only at lower transmural pressure gradients (9–18 mmHg).
Third, CFC in elderly but not in young women increased at higher transmural pressure gradients (36 mmHg),
indicating an increased capillary susceptibility to transmural
pressure load in dependent regions in the elderly.

We recently examined lower limb venous compliance
in young women and men, using similar technique as in this study
(26) and found a decreased venous compliance and capacitance
in women, in analogy with earlier studies (30, 34). The differences
between sexes were striking at low transmural pressures,
but with increasing pressure, the sex difference in venous compliance decreased and, at transmural pressures relevant to
quiet standing or head-up tilt, women may in fact have a higher
venous compliance than men (26). The underlying factors
behind the sex difference in venous compliance are at present
unknown. The effect of oral contraceptives on calf venous
compliance and capacitance was, however, insignificant (see
RESULTS), in agreement with Meendering et al. (30).

Calf venous compliance is reduced with age in men, which
increases the possibility to resist an orthostatic challenge due to
smaller reduction in thoracic blood volume and cardiac filling
volumes (25, 33, 38, 39, 49), although this relationship has
recently been challenged (18). The decreased venous compli-
ance and capacitance are probably an effect of increased
collage-to-elastin ratio as well as thickening of the venous
walls, corresponding to the known structural changes and a
decrease in arterial wall compliance with age (3, 9, 48).
However, as discussed by Hernandez and Franke (18), there is
reason to believe that the age-related changes in venous com-
pliance and capacitance may be modified by sex difference.
This may be due to differences in hormonal influence as shown in
arteries, with women having a slower decrease in arterial
compliance with age compared with men (9, 48). Estrogen has
been shown to affect cellular transcription of elastin and
collagen, and estrogen receptors are known to exist in vascular
smooth muscle cells (21, 22, 32). However, so far little atten-
tion has been paid to this hypothesis.

Our study seems to be the first to evaluate age-related
changes in venous compliance of women, and we found no
age-related changes in venous compliance or capacitance. With
increasing transmural pressure, venous compliance decreased in
a similar fashion in elderly and young women (Fig. 2, A and
B). This absence of age-related changes in women could be a
result of several factors. The slightly larger BMI in the elderly
might lead to differences in soft tissue-to-bone ratio between
the groups. This could lead to an overestimation of the capa-
tiance response in the elderly women; however, this seems
unlikely since the difference in BMI was small (Table 1).
Although both elderly and young women were of average
physical fitness, the elderly women may still have been more
unfit. Sedentary subjects have lower calf venous compliance,
and this would work in favor of detecting a putative reduction
in venous compliance with age in women (18, 33). Another
confounder might be differences in venous filling before
LBNP, i.e., unstressed volume ($V_0$). No measurement of $V_0$
in the calf was made before LBNP, and there is no reason to
believe that $V_0$ is constant. To avoid inappropriate differences
in $V_0$ between individuals, care was taken to place the mid-
point of the calf 5 cm below heart level in all subjects.

Furthermore, the subjects rested in the supine position for a
long enough time to ensure stable $V_0$ before institution of
LBNP. The time to 50% of the venous capacitance response in
the calf to be developed ($C_{cap}$) as well as the change in P-NE,
FBC, and FVC during LBNP was equivalent between elderly
and young women (Table 2). This indicates a similar decrease
in pressure gradient from capillaries to large veins as well as
small vein pressure (41), and, accordingly, no difference in $\beta_0$
between young and elderly women was found. Finally, the
inclusion of capillary filtration might introduce an error in calf
venous compliance calculations (see RESULTS), in analogy with
previous findings (26). This was evaded by separating venous
capacitance and capillary fluid filtration before compliance
calculations (see METHODS). All in all, the conclusion that
venous compliance is not reduced with age in women seems
credible (Fig. 2B). Furthermore, this implies that men and
women should be separated when studying age-related effects
on venous compliance.

In accordance with our earlier findings, CFC in the calf of
young women was 0.004–0.005 ml·100 ml$^{-1} \cdot$min$^{-1} \cdot$mmHg$^{-1}$
and was unaffected by changes in transmural pressure (Fig. 4,
A and B) (26). This is in agreement with Bentzer et al. (1),
using similar technique as ours (negative tissue pressure) in a
cat model, who found CFC to be independent of the number of
perfused capillaries. However, the common view is that CFC is
influenced by variations in the number of perfused capillaries
due to local myogenic as well as axon reflex responses reacting
on transmural pressure changes in the microcirculation (11, 17,
29, 44). Thus CFC in our study may have decreased from its
basal level by not only a local increase in transmural pressure
but also an increased sympathetic discharge in response to the
reduced central blood volume during LBNP, leading to an
increase in pre-to-postcapillary resistance ratio and a concom-
itant decrease in capillary pressure as well as an opening of
precapillary sphincters due to sympathetic activation (24, 31).
This potential error seems to be insignificant, however, since
no change in CFC was found in young women despite sub-
stantial changes in transmural pressure as well as FVC during
the applied LBNP levels (Fig. 4B and Table 2). Furthermore,
CFC in the calf in young women seems to be higher than in
young men (26). This is in accordance with findings by Huxley
et al. (20) who studied coronary microvessel permeability in a
large animal model and found an increased permeability to
proteins in venules in females after an administration of aldo-
sterone (20). The increased capillary filtration may be ex-
plained by higher levels of estrogen in women and its effect on

| Table 2. Decrease in FBF and FVC in elderly and young women during LBNP |
|-----------------|-------|-------|-------|-------|
|                  | 11 mmHg | 22 mmHg | 44 mmHg |
| Elderly women    |     |     |     |     |
| FBF, %           | 90±4 | 85±3 | 74±4* |
| FVC, %           | 89±3 | 81±2 | 73±4* |
| Young women      |     |     |     |     |
| FBF, %           | 94±3 | 93±4 | 84±4* |
| FVC, %           | 94±3 | 89±5 | 79±4* |

Values are means ± SE. FBF and FVC during lower body negative pressure
(LBNP) in elderly and young women (in % of basal value) are shown. FBF and
FVC decreased with increasing LBNP. *P < 0.05. There were no differences
in FBF or FVC with age.
the microcirculation (45). Tollan et al. (47) proposed a direct effect of estrogen on capillary protein permeability, which increases filtration capacity. Furthermore, the vasodilatory effect of estrogen may increase capillary pressure and facilitate capillary filtration (19). Atrial natriuretic peptide (ANP) affects capillary filtration by increasing CFC and/or protein permeability (14, 50), and estrogen augments the ANP effect on CFC (45).

To the best of our knowledge, no earlier studies on age-related changes in CFC of women have been carried out. CFC was reduced by ~28% in elderly compared with young women during an increase of 9 and 18 mmHg in transmural pressure (Fig. 4A). A defective transmission of negative pressure into the tissue would result in a reduction of the estimated CFC. However, transmission of negative pressure into the calf is not affected by age (38), further supported by the similar capacitance response in the calf of the elderly compared with the young women during LBNP (Fig. 2A). Another factor of importance might be a delayed capacitance response with age due to a slower pressure change in the tissue caused by a decrease in viscoelasticity of the calf skeletal muscle as shown in men (38). This seems refuted by the fact that the time to 50% of the capacitance response to be developed during LBNP was equal in elderly and young women. Also, if a decrease in viscoelasticity would still be present, a delayed capacitance response in the elderly beyond the applied cut-off point between capacitance response and filtration (3 min after initiation of LBNP) would result in an overestimation of CFC in the elderly women, indicating a larger difference in CFC than presented in this study. Thus the conclusion that CFC is decreased in elderly women seems to be valid. All of the elderly women were in a postmenopausal, estrogen-deficient state (2). Because of the direct and indirect effect of estrogen on capillary permeability to proteins as well as the vasodilatory effects of estrogen, it seems reasonable to assume that this is one of the main mechanisms for the reduction in CFC with age (14, 19, 45, 47, 50). This is corroborated by the fact that women taking hormone replacement therapy improve their endothelial function and increase their basal limb blood flow to a premenopausal level (35, 42). Furthermore, the reduction in CFC found in postmenopausal women is down to the level found in men (also low estrogen levels), in whom no age-related effect on CFC has been found (2, 25). The reactivity of the arterioles seems to be impaired due to changed cellular mechanisms with endothelial and smooth muscle dysfunction, which might induce heterogeneity in flow between different capillaries (36). Furthermore, capillary density in skeletal muscle is also reduced with age, and capillary basement membranes thicken in dependent regions because of long-lasting increases in capillary pressure, indicating a loss of capillary function (4, 8, 16). The experimental setup, however, prevents us from distinguishing between the effect of decreased estrogen levels and age-related structural differences on CFC.

An interesting observation was that CFC was augmented by ~1/3 when increasing the applied transmural pressure change from 18 to 36 mmHg in the elderly women (Fig. 4A and B). Increased fluid permeability at high microvascular transmural pressures has been reported by several authors working on vascular bed preparations in isolated limbs as well as on single microvessels (37, 40, 51). These observations have been interpreted as the stretched pore phenomenon, caused by passive stretching of the microvascular membrane with the formation of gaps in or between endothelial cells, preferentially in the venules where the interendothelial junctions appear to be less tight than in the true capillary section (12). Another possibility is that the imposed pressure distension more efficiently opens all microvessels to flow (40). The stretched pore phenomenon has been shown to be reversible with time after the reduction of high microvascular pressure and capillary filtration was normalized (37, 40, 51). Most studies have shown capillary walls to tolerate pressure elevations far beyond their physiological range without an increase in permeability, and it is, at present, unknown as to whether capillary walls become more fragile or if cellular junctions in the microvessels become less tight with age. The increasing CFC at higher transmural pressure in the lower limbs of elderly women might give additional insight into the preponderance of leg oedema besides earlier known factors such as cardiac and venous insufficiency. This surely deserves further attention.

In conclusion, calf venous compliance and capacitance did not change with age in healthy women and implies that age-related changes in venous compliance and capacitance are modified by sex, since a reduction in venous compliance and capacitance has earlier been shown in men (33, 38, 39, 49). Thus men and women should be studied separately when analyzing age-related effects on venous compliance. Furthermore, interstitial fluid accumulation due to capillary fluid filtration was reduced in elderly women, probably due to lower CFC than in the young women. This was, however, evident only at lower transmural pressure gradients. CFC in elderly but not in young women increased at higher transmural pressure gradients, indicating an increased capillary susceptibility to transmural pressure load in dependent regions in the elderly.

GRANTS

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REFERENCES