Reduced venous compliance: an important determinant for orthostatic intolerance in women with vasovagal syncope

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1Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; 2Department of Cardiology, Linköping University, Linköping, Sweden; 3Ekman Biomedical Data, Göteborg, Sweden; 4Department of Clinical Physiology, Linköping University, Linköping, Sweden; and 5Department of Thoracic and Vascular Surgery, Linköping University, Linköping, Sweden

Submitted 18 August 2015; accepted in final form 9 November 2015

Skoog J, Lindenberger M, Ekman M, Holmberg B, Zachrisson H, Länne T. Reduced venous compliance: an important determinant for orthostatic intolerance in women with vasovagal syncope. Am J Physiol Regul Integr Comp Physiol 310: R253–R261, 2016. The influence of lower limb venous compliance on orthostatic vasovagal syncope (VVS) is uncertain. The most widespread technique to calculate venous compliance uses a nonphysiological quadratic regression equation. Our aim was therefore to construct a physiologically derived venous wall model (VWM) for calculation of calf venous compliance and to determine the effect of venous compliance on tolerance to maximal lower body negative pressure (LBNP). Venous occlusion plethysmography was used to study calf volume changes in 15 women with VVS (25.5 ± 1.3 yr of age) and 15 controls (22.8 ± 0.8 yr of age). The fit of the VWM and the regression equation to the experimentally induced pressure-volume curve was examined. Venous compliance was calculated as the derivative of the modeled pressure-volume relationship. Graded LBNP to presyncope was used to determine the LBNP tolerance index (LTI). The VWM displayed a better fit to the experimentally induced pressure-volume curve (P < 0.0001). Calf blood pooling was similar in the groups and was not correlated to the LTI (r = 0.204, P = 0.30). Venous compliance was significantly reduced at low venous pressures in women with VVS (P = 0.042) and correlated to the LTI (r = 0.459, P = 0.014) in the low pressure range. No correlation was found between venous compliance at high venous pressures and the LTI. In conclusion, the new VWM accurately adopted the curvilinear pressure-volume curve, providing a valid characterization of venous compliance. Reduced venous compliance at low venous pressures may adversely affect mobilization of peripheral venous blood to the central circulation during hypovolemic circulatory stress in women with VVS.

Vasovagal syncope (VVS), with a lifetime cumulative incidence of 25–40%, is the most common type of syncope (12). The majority of vasovagal episodes are seen in adolescents and young adults, and VVS is more common in women than men (3). Despite numerous investigations, the mechanisms by which the vasovagal reaction is initiated remain elusive. A paradoxical loss of sympathetic activity and increased vagal tone, leading to vasodilation and a decrease in heart rate, have for a long time been considered a key factor (7, 35, 55).

However, recent studies have shown that withdrawal of muscle sympathetic nerve activity is not a prerequisite for the dramatic drop in blood pressure during the vasovagal reaction (5, 9, 53). Instead, a successive fall in cardiac output has been suggested as an alternative trigger (9, 54). The reason for the decrease in cardiac output during orthostatic stress is not known, but a progressive impairment of venous return has been proposed (11, 26, 27, 54).

A transition to upright posture leads to a gradual increase in venous pooling in the lower extremities (14). This is followed by a concomitant decrease in thoracic blood volume and venous return, which instantly challenges blood pressure control (14, 39). Greater leg venous compliance has been suggested to increase the vulnerability to orthostatic stress as a result of greater reductions in venous return and stroke volume (16, 28, 52), although this has been refuted by Hernandez and Franke (20). Freeman et al. (8) reported lower venous compliance in patients with idiopathic orthostatic intolerance. Lower venous compliance could lead to reduced mobilization of capacitance blood, further aggravating the reduction in venous return and triggering the vasovagal reaction (23, 54). Methodological difficulties could, to some extent, explain the conflicting results. In these studies, venous compliance was determined after several minutes of venous stasis without separation of venous blood pooling from the prominent net fluid filtration. We recently demonstrated that this can lead to misinterpretations, since net fluid filtration significantly affects venous compliance (44). Present assessments commonly use a mathematically derived quadratic regression equation (QRE) to model the venous pressure-volume curve and the first derivative of this equation to characterize venous compliance. With this approach, venous compliance is bound to become negative at a pressure within or very close to the applied physiological pressure range, precluding a valid interpretation (13, 17, 32–34, 43).

Venous compliance has not been accurately measured in a well-defined VVS population, although lower limb venous pooling may be of pathophysiological importance. The aim of the present study was, therefore, 1) to introduce and validate a new physiologically derived three-parameter venous wall model (VWM) for the characterization of the venous pressure-volume relationship and 2) to accurately study calf venous compliance (C_{calf}), as well as the calf venous capacitance (V_{cap}) response (blood pooling), and assess its impact on orthostatic tolerance to lower body negative pressure (LBNP) in women diagnosed with VVS and matched controls. We hypothesized that the new physiologically derived
model would provide a valid assessment of venous compliance and that venous compliance would be lower in women with VVS.

MATERIALS AND METHODS

Participants

The study was approved by the Regional Ethical Review Board in Linköping, Sweden, and all subjects signed a written informed consent in conformity with the Declaration of Helsinki. A total of 30 women participated in the study; 15 of the women (25.5 ± 1.3 yr of age), with a history of syncope, had previously been referred to Linköping University Hospital and diagnosed with VVS after a typical, positive response to a head-up tilt test. A positive head-up tilt test was defined as symptoms and signs of impending syncope accompanied by arterial hypotension, bradycardia, or both. Subjects with a cardiovascular and/or neurological disease were excluded. All participants with VVS reported at least one episode of syncope in the year preceding the study (Table 1). The control group consisted of 15 healthy women (22.8 ± 0.8 yr of age), with no history of syncope, recruited by means of public advertising at Linköping University. All participants were nonsmokers, and none were taking medication, except for different contraceptives, which were used by seven VVS subjects. All testing was scheduled within the follicular phase of the menstrual cycle or early contraceptive phase (days 1–10). All subjects were asked to abstain from caffeine and nicotine on the day of laboratory testing and to avoid vigorous-intensity activity on the day before the test. All subjects were also instructed to abstain from alcohol and to ingest 1 liter of water on the evening before the experiment.

Venous Occlusion Plethysmography

Changes in venous volume were measured with strain gauge plethysmography. Recordings were performed in a temperature-stable (25°C) room. Subjects were placed in the supine position, with the right leg slightly elevated and supported at the ankle, and allowed ≥15 min for acclimation. A strain gauge was applied at the maximal calf circumference and manually calibrated. A cone-shaped, 22-cm-wide thigh cuff was placed on the thigh proximal to the knee on the right leg. A cuff inflator (Bergenheim, Elektromedicin, Göteborg, Sweden) was used to inflate the thigh cuff to 60 mmHg within 1 s. A wide thigh cuff was placed on the thigh proximal to the knee on the right leg. After 8 min, cuff pressure was reduced at a rate of 1 mmHg/s by a custom-built device, enabling a linear pressure decrease. The calf cuff pressure-venous pressure relationship is less reliable below 10 mmHg, and these data were excluded from the analysis (44). All data were recorded, stored, and analyzed using PeriVasc software (Ekman Biomedical Data, Göteborg, Sweden).

Table 1. Demographic resting values in VVS and control subjects

<table>
<thead>
<tr>
<th></th>
<th>VVS</th>
<th>Controls</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>25.5 ± 1.3</td>
<td>22.8 ± 0.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164 ± 1.9</td>
<td>167 ± 1.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62 ± 2.5</td>
<td>64 ± 2.9</td>
<td>0.49</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.7 ± 0.8</td>
<td>22.9 ± 1</td>
<td>0.87</td>
</tr>
<tr>
<td>Calf circumference, cm</td>
<td>36.2 ± 0.8</td>
<td>35.6 ± 0.7</td>
<td>0.60</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>66 ± 2.7</td>
<td>67 ± 2.6</td>
<td>0.62</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>104 ± 3.9</td>
<td>111 ± 3</td>
<td>0.19</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>63 ± 2.2</td>
<td>65 ± 1.9</td>
<td>0.43</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>76 ± 3.9</td>
<td>82 ± 2.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Syncope history, yr</td>
<td>7.0 ± 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope recurrence, n</td>
<td>≥1 per year</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥1 per month</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥1 per week</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE of 15 subjects in each group. VVS, vasovagal syncope; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

volume to the maximum volume stored in the veins at the given pressure (V_cap response), followed by a slower increase caused by net fluid filtration. We recently showed that V_cap is completed within 3–4 min when cuff pressure is elevated to 60 mmHg (44). Net fluid filtration (ml/100 ml⁻¹·min⁻¹) was therefore calculated as the slope of the volume curve between 4 and 8 min, and V_cap (ml/100 ml) was obtained by a backward extrapolation of the filtration slope to the onset of venous occlusion plethysmography (VOP) (29). Net fluid filtration is also a confounder when C_cap is evaluated during VOP; to avoid this, a correction model subtracted net fluid filtration from the total calf volume changes as described by Skoog et al. (44). Briefly, an accumulated filtration volume was established on the basis of the filtration rate, and this volume was then subtracted from the original volume curve (Fig. 1A). C_cap (ml/100 ml⁻¹·mmHg⁻¹) was calculated from the pressure-volume relationship during the deflation phase (Fig. 1B). The calf cuff pressure-venous pressure relationship is less reliable below 10 mmHg, and these data were excluded from the analysis (44).
Venous Compliance

Venous compliance is defined as a change in volume (∆V) generated by a change in venous transmural pressure (∆P); i.e., venous compliance (ΔV/ΔP) denotes the slope of the tangent at any point along the pressure-volume relationship (42). At low transmural pressures, the pressure-volume curve is steep, indicating a high compliance, which means that only a small increase in transmural pressure is followed by a relatively large change in volume. At higher pressures, the pressure-volume curve is flatter; thus, compliance is lower (41). The expansion of the veins at low transmural pressures (<10 mmHg) is also related to changes in geometry, i.e., a transformation from an elliptical to a circular cross section (37). At higher pressures, the volume change is dependent on the elastic properties of the venous wall. The venous wall consists of elastin, collagen, and smooth muscle in which the highly elastic elastin fibers are the first to be engaged during tension of the vessel; this is followed by a gradual recruitment of the collagen fibers, which acts to stiffen the venous wall and limit further increase in the circumference (41, 42). As such, the venous pressure-volume curve is characterized by two functional features. 1) It enables large translocations of blood from peripheral capacitance veins at low venous pressures in response to small pressure changes and, thereby, increases cardiac filling, e.g., during acute hypovolemia. 2) It minimizes venous pooling and the concomitant central hypovolemia at high venous pressures during upright posture (41, 42).

VWM. The VWM was constructed as a three-parameter model that describes the relationship between the transmural pressure and the vessel radius. This was achieved by modeling the vessel wall stiffness as a function of the radius. The primary aim of the VWM was to mimic the volume dynamics associated with changes in transmural pressure. On this basis, the radius and the vessel wall stiffness are quantities of arbitrary units (AU), while the transmural pressure is expressed as mmHg. Thus, to obtain an accurate fit of the VWM volume range, the model was adjusted to the same volume span as the experimentally induced pressure-volume curve. The model parameters of a fictitious vein/venous system per unit length with a radius of 1 (AU) for pressure = 0 (mmHg) are described as follows: \( \gamma_0 \) (AU) represents the initial stiffness of the vessel wall at pressure = 0 mmHg, hence, the radius = 1; \( \gamma_d \) (AU) represents the initial increase in vessel wall stiffness as a function of the radius extension/increase; and \( R_{max} \) (AU) represents the maximal radius/circumference, obtained by letting the wall stiffness approach infinity as the radius approaches \( R_{max} \).

An equilibrium is assumed to be present between the expansive forces of the vessel and the opposing tensile forces of the vessel wall expansive force \( \sim (P \cdot R) \) (1)

tensile force \( \sim (R - R_0) \cdot \eta(R) \) (2)

where \( P \) denotes the transmural pressure (mmHg), \( R \) is the radius (AU), \( R_0 \) is the radius at 0 mmHg pressure, i.e., \( R_0 = 1 \) AU, and \( \eta(R) \) is the vessel wall stiffness as a function of \( R \) (AU). The equilibrium between the expansive and the tensile force results in

\[ P \cdot R \sim (R - R_0) \cdot \eta(R) \] (3)

To construct the VWM, several functions for the vessel wall stiffness, i.e., \( \eta(R) \) (AU), were developed and evaluated. The general requirements were that the model should contain three basic physiological parameters: 1) \( \gamma_0 \), 2) \( \gamma_d \) increase in wall stiffness as a function of the radius, and 3) \( R_{max} \) (infinite wall stiffness). On this basis, the VWM was constructed as a model of \( \eta(R) \) (AU), comprising two terms. The first term determines the initial part of the venous pressure-volume curve by the parameter \( \gamma_0 \) (AU). The second term determines the progress of the vessel stiffness as a function of the radius by the parameter \( \gamma_d \) (AU) and the asymptotic limit of the increase in radius by the parameter \( R_{max} \) (AU). Accordingly, \( \eta(R) \) (AU) is defined as

\[ \eta(R) \sim R \cdot \left[ \gamma_0 + \gamma_d \cdot \left[ \frac{(R_{max} - R_0)}{(R_{max} - R)} - 1 \right] \right] \] (4)

The radius-dependent vessel wall stiffness, i.e., \( \eta(R) \) (AU), can therefore be modified by altering the model parameters \( \gamma_0 \), \( \gamma_d \), and \( R_{max} \) (AU) (Fig. 2A). According to Eq. 3 and our model for the vessel stiffness \( \eta(R) \) (AU), \( P \) (mmHg) is related to \( R \) (AU) as follows

\[ P \sim (R - R_0) \cdot \eta(R) \] (5)

Insertion of Eq. 4 into Eq. 5 results in

\[ P \sim (R - R_0) \cdot \gamma_d \cdot \left[ \frac{(R_{max} - R_0)}{(R_{max} - R)} - 1 \right] / R \] (6)

with \( R_0 = 1 \) (AU), Eq. 7 simplifies to

\[ P \sim (R - 1) \cdot \gamma_d \cdot \left[ \frac{(R_{max} - 1)}{(R_{max} - R)} - 1 \right] \] (7)

which describes the pressure-radius relationship, \( P(R, \gamma_0, \gamma_d, R_{max}) \), generated from a given set of model parameters \( \gamma_0 \), \( \gamma_d \), and \( R_{max} \). By using a given set of model parameters \( \gamma_0 \), \( \gamma_d \), and \( R_{max} \), the

Fig. 2. Influence of model parameters on the venous wall model (VWM). A: radius-dependent vessel wall stiffness \( \eta(R) \) can be modified by altering the model parameters \( \gamma_0 \) (initial stiffness of the vessel wall at pressure = 0 mmHg), \( \gamma_d \) (initial increase in vessel wall stiffness as a function of the radius extension/increase), and \( R_{max} \) (maximal radius/circumference). \( \gamma_0 = 350, \gamma_d = 50, \) and \( R_{max} = 1.1 \) are used as reference values for \( \eta(R) \) (solid black line). Effects of decreasing \( \gamma_0 \) from 350 to 250 illustrate a reduction in initial stiffness of the vessel wall (solid gray line). Effects of increasing \( \gamma_d \) from 50 to 150 illustrate progress in development of vessel wall stiffness (dotted black line). Effects of increasing \( R_{max} \) from 1.1 to 1.15 illustrate an extension of the asymptotic limit determined by the maximal radius increase (dotted gray line). B: shape of the curvilinear venous pressure-volume relationship can be adjusted by altering the model parameters \( \gamma_0 \), \( \gamma_d \), and \( R_{max} \). The pressure-volume relationship with parameters \( \gamma_0 = 350, \gamma_d = 50, \) and \( R_{max} = 1.1 \) are used as reference values (solid black line). Solid gray line shows effects of decreasing \( \gamma_0 \) from 350 to 250. Dotted black line shows effects of increasing \( \gamma_d \) from 50 to 150. Dotted gray line shows effects of increasing \( R_{max} \) from 1.1 to 1.15.
 pressure-radius relationship can be transformed to a pressure-volume relationship by squaring the radius, \( P(R^2, \eta_0, \eta_0, R_{max}) \), and by altering the model parameters, the shape of the curvilinear venous pressure-volume relationship can be adjusted (Fig. 2B). This corresponds to the theoretical considerations applicable to the measurement of volume changes with strain gauge plethysmography (56). To find the correct model parameters for the experimentally constructed pressure-volume curve, a numerical algorithm is required. We used the downhill simplex algorithm with least-squares deviation from raw data as an error function in search of the model parameters \( \eta_0, \eta_0, \) and \( R_{max} \) (AU). \( C_{calf} \) for pressure P was calculated as the numerical derivative of the pressure-volume curve generated by the VWM. This was conducted over a pressure range of 2 mmHg (1 mmHg below P and 1 mmHg above P) for pressures between 10 and 60 mmHg with a 5-mmHg interval. Thus, if volume for pressure P is \( V(P) \), then \( C_{calf} \) is defined as

\[
C_{calf} = \frac{[V(P + 1 \text{ mmHg}) - V(P - 1 \text{ mmHg})]}{2} \quad (9)
\]

The characteristics of the volume-pressure curves were described by the established QRE, which is a strict mathematical sure-compliance curve. The first derivative of the pressure-volume curve, creating a linear pressure-volume relationship can be adjusted (Fig. 2). Thus, if volume for pressure P is \( V(P) \), then \( C_{calf} \) is defined as

\[
\Delta \text{volume} = \beta_0 + \beta_1 \cdot (\text{cuff pressure}) + \beta_2 \cdot (\text{cuff pressure})^2 \quad (10)
\]

where \( \beta_0 \) is the y-intercept and \( \beta_1 \) and \( \beta_2 \) are characteristics of the slope generated by the pressure-volume curve. \( C_{calf} \) was defined as the first derivative of the pressure-volume curve, creating a linear pressure-compliance curve

\[
C_{calf} = \beta_0 + 2 \cdot \beta_2 \cdot (\text{cuff pressure}) \quad (11)
\]

By using Eq. 11, \( C_{calf} \) was calculated for pressures between 10 and 60 mmHg with a 5-mmHg interval. To evaluate the fit of the VWM and the QRE, the mean deviance (ml/100) from the pressure-volume raw data curve was calculated at each 5-mmHg (±2 mmHg) step between 15 and 55 mmHg.

Lower Body Negative Pressure

Each subject was placed in the supine position in a LBNP chamber that was hermetically sealed at the level of the iliac crest. Application of LBNP redistributes blood from the lower body to the upper extremities, leading to central hypovolemia (5). The negative pressure in the LBNP chamber was generated by a vacuum source, constantly measured by a manometer (DT-XX disposable transducer, Viggo Spectramed, Helsingborg, Sweden), and held constant by a rheostat. After ≥15 min of rest, the LBNP chamber pressure was reduced by 20 mmHg for 4 min. Subsequently, pressure was reduced in 10-mmHg increments every 4 min. The test was terminated according to the following criteria: 1) after completion of 4 min of 70 mmHg LBNP, 2) at the onset of presyncopal signs or symptoms (a ≥25-mmHg decrease in systolic blood pressure between adjacent 1-min readings, a ≥15-mmHg decrease in diastolic blood pressure between adjacent 1-min readings, a sudden ≥15 beats/min decrease in heart rate, nausea, pallor, profuse sweating, or dizziness); or 3) at the subject’s request. LBNP tolerance was calculated as LBNP tolerance index (LTI). LTI was the product of time spent at each LBNP level and the magnitude of the pressure reduction from the previous completed LBNP stage. In the present study, the LTI describes the LBNP tolerance as a linear function. All controls participated in the LBNP protocol, but one VVS subject was unable to participate.

Heart Rate and Blood Pressure

Heart rate and blood pressure at rest were measured noninvasively using a semiautomatic blood pressure cuff positioned over the brachial artery on the right upper arm (Dinamap Pro 200 Monitor, Criticon, Tampa, FL). Heart rate and blood pressure during the LBNP protocol were monitored noninvasively, beat-by-beat (Finometer Midi, Finapres Medical Systems, Amsterdam, The Netherlands).

Physical Activity

To evaluate physical activity, we used the short version of the International Physical Activity Questionnaire (IPAQ-short), which is an established self-report physical activity instrument (6). The IPAQ-short asks for information about three types of physical activity (walking, moderate activity, and vigorous activity). In addition, each activity corresponds to a metabolic equivalent (MET), producing a score in MET-minutes (MET describes the metabolic rate of each activity) and, thereby, providing an evaluation of physical activity (20a).

Statistical Analyses

Values are means ± SE unless otherwise stated. Repeated-measures ANOVA with Bonferroni’s correction for multiple comparisons was used to compare the model’s ability to fit the experimentally induced pressure-volume curve, as well as to compare pressure-compliance curves between the two models. Repeated-measures ANOVA was also used to compare the pressure-volume and pressure-compliance curves between groups. Group differences in \( V_{cap} \) and net fluid filtration were tested by an unpaired Student’s t-test. The Mann-Whitney test was used to compare levels of physical activity. Linear regression analysis was used to determine the association between \( C_{calf} \) at low and high venous pressures, as well as \( V_{cap} \) in respect to LTI. \( P < 0.05 \) was considered statistically significant. Statistical analyses were carried out using SPSS 22.0 for Windows (SPSS, Chicago, IL).

RESULTS

Subject Characteristics

Table 1 shows baseline characteristics of VVS and control subjects. Age, anthropometric data, heart rate, and blood pressure were similar between the groups. Eighty percent of VVS subjects experienced symptoms related to VVS at least once a month, and the mean syncope history was 7.0 ± 1.0 yr. The median (25th–75th percentile) of total physical activity was 3,600 (range 803–5,071) and 2,510 (range 1,758–3,186) MET-min/wk in VVS and control subjects, respectively [not significant (\( P = 0.22 \)].

Characterization of the VWM and the QRE

Figure 3A depicts the QRE fit to a representative original pressure-volume curve during the deflation phase (cuff pressure reduction of 1 mmHg/s) after 8 min of VOP. The QRE reached its vertex at ~50 mmHg and, consequently, was unable to model further volume increases in the venous pressure-volume curve. Figure 3B depicts the VWM fit to the same original pressure-volume curve. The VWM was able to adopt the curvilinear form of the venous pressure-volume relationship over the entire pressure range. Figure 3C shows cumulative data of the deviation from the pressure-volume raw data in the QRE and VWM. The VWM showed a significantly better fit to the experimentally induced pressure-volume curve than the QRE [\( P < 0.0001 \) (interaction); \( P < 0.0001 \), VWM vs. QRE]. Figure 3D shows the pressure-compliance relationship calculated from the QRE and the VWM. The pressure-compliance curve showed a steeper negative slope at high venous pressures when calculated...
with the QRE, and \(C_{calf}\) was underestimated \([P = 0.039\) (interaction)]. Furthermore, \(C_{calf}\) was characterized by a linear slope when calculated with the QRE, whereas the slope of the VWM was sigmoidal in nature. \(C_{calf}\) became negative at the highest pressures when calculated with the QRE. This was demonstrated in three subjects \((10\%)\) at 55 mmHg and in 22 subjects \((73\%)\) at 60 mmHg. No negative values of \(C_{calf}\) were generated with the VWM.

The parameters of the QRE were \(0.016 \pm 0.081\) \((\beta_0)\), \(0.088 \pm 0.005\) \((\beta_1)\), and \(-0.00075 \pm 0.00024\) \((\beta_2)\). The parameters of the VWM were \(393 \pm 69\) \((\eta_0)\), \(56.6 \pm 7.6\) \((\eta_1)\), and \(1.14 \pm 0.15\) \((R_{max})\).

**Calf Volume Responses**

No differences were seen in the \(V_{cap}\) response: \(2.26 \pm 0.19\) and \(2.63 \pm 0.18\) \((ml/100 \text{ ml})\) in VVS and control subjects, respectively \((P = 0.16)\). Net fluid filtration was \(0.175 \pm 0.012\) and \(0.184 \pm 0.012\) \((ml/100 \text{ ml}^{-1} \text{ min}^{-1})\) in VVS and control subjects, respectively \([\text{not significant} \ (P = 0.60)]\). The VWM, which is more accurate than the QRE, was used in the following comparison of the pressure-volume and pressure-compliance curves between VVS and control subjects. Figure 4A shows the pressure-volume relationship in VVS and control subjects during VOP, with VVS subjects presenting a significantly less steep curve \([P = 0.047\) (interaction)]. Figure 4B shows the corresponding \(C_{calf}\) curves, with reduced \(C_{calf}\) in VVS subjects compared with controls \([P = 0.022\) (interaction); \(P = 0.042\), VVS vs. control]. Figure 4C shows \(C_{calf}\) at low venous pressures, where VVS subjects displayed reduced \(C_{calf}\) \((P < 0.05)\). For example, \(C_{calf}\) was 23% lower at 20 mmHg in VVS subjects, while at higher pressures the compliance curves approached each other and finally merged at \(\sim 50\) mmHg. Figure 5 displays the \(V_{cap} \cdot C_{calf}\) relationship (calculated as the mean value from 10 to 60 mmHg in each subject). \(C_{calf}\) showed a strong positive correlation to \(V_{cap}\) \((r = 0.848, P < 0.0001)\).

The parameters of the VWM were \(391 \pm 28\) \((\eta_0)\), \(69.5 \pm 9.5\) \((\eta_1)\), and \(1.10 \pm 0.01\) \((R_{max})\) in VVS subjects and \(395 \pm 138\) \((\eta_0)\), \(43.6 \pm 11.2\) \((\eta_1)\), and \(1.18 \pm 0.02\) \((R_{max})\) in controls.

**LBNP Tolerance**

No participant requested termination of the LBNP protocol. For all VVS subjects, presyncopal signs or symptoms resulted in termination of the LBNP protocol, whereas two control subjects completed the entire protocol. One VVS subject developed signs of syncope within the first minutes of 20 mmHg LBNP, and no LTI could be calculated. LTI was reduced in VVS subjects compared with controls \((163 \pm 8 \text{ vs. } 235 \pm 8 \text{ DmmHg/min}, P < 0.0001)\). Figure 6A shows the LTI-\(C_{calf}\) relationship (at 20 mmHg) in all subjects pooled. \(C_{calf}\) at 20 mmHg was positively correlated to LTI \((r = 0.459, P = 0.014)\). No correlation was found between LTI and \(C_{calf}\) at 60 mmHg \((r = 0.292, P = 0.131)\). Figure 6B shows the LTI-\(V_{cap}\) relationship in all subjects pooled. There was no correlation between \(V_{cap}\) and LTI \((r = 0.204, P = 0.30)\).

**DISCUSSION**

A new physiologically derived VWM was constructed for calculation of \(C_{calf}\) in women with VVS and matched controls. The main findings include the following. 1) The VWM provided a more valid characterization of the entire venous pressure-volume relationship than the widely used QRE. 2) \(C_{calf}\) at high venous pressures was comparable in VVS and control subjects, resulting in a similar \(V_{cap}\), with no correlation between \(V_{cap}\) and LBNP tolerance. 3) \(C_{calf}\) at low venous pres-
sures was significantly reduced in VVS subjects, and reduced compliance in the low pressure range was associated with a decreased LBNP tolerance.

**VWM vs. QRE**

We recently investigated the impact of net fluid filtration on \( C_{\text{calf}} \) calculated with the QRE and found that some of the subjects displayed a nonphysiological negative \( C_{\text{calf}} \) in the high pressure range (44). Accordingly, the present study revealed that 10% of the subjects at 55 mmHg and 75% of the subjects at 60 mmHg displayed a negative \( C_{\text{calf}} \) calculated with the QRE. Thus the major limitation with the QRE is in the high pressure range and could likely be explained by the mathematically applied quadratic function, which, in the majority of cases, reaches its vertex within the investigated pressure range (Fig. 3A). Because of the form of the venous pressure-volume curve, it appears to be of great importance to model the whole curve accurately, especially since gravitational forces could increase venous pressure well above 60 mmHg during prolonged standing. It is possible that a higher-order function could adopt the pressure-volume curve better than a quadratic function. However, all these functions share the same inherent problem: they do not possess the basic shape of the venous pressure-volume curve. Hence, we wanted to construct a model that asymptotically follows the curvilinear form of the pressure-volume curve. Another possibility would be a discrete approach, as described by Freeman et al. (8), where compliance was calculated as the numerical derivative of each pressure-volume raw data point. The major limitation of this technique is that it is particularly sensitive to measurement artifacts. From this point of view, it seems more reliable to use a continuous model.

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**Fig. 4.** Pressure-volume and pressure-compliance relationships in VVS and control subjects. A: volume curve was less steep in VVS (○) than control (■) subjects \([P = 0.047 \text{ (interaction)}]\). B: venous compliance was significantly lower in VVS subjects \([P = 0.022 \text{ (interaction)}; P = 0.042, \text{VVS vs. control}}\]. C: closer view at low venous pressures, where VVS subjects display reduced venous compliance. VVS vs. control: *\( P < 0.05 \), **\( P < 0.01 \).

**Fig. 5.** Correlation between calf venous capacitance \((V_{\text{cap}})\) response and \( C_{\text{calf}} \). \( C_{\text{calf}} \) calculated as the mean value in each subject [VVS (○) and control (■)] was highly correlated to the \( V_{\text{cap}} \) response.

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**Fig. 6.** Correlations between lower body negative pressure tolerance index \((\text{LTI})\) and \( C_{\text{calf}} \). \( C_{\text{calf}} \) at 20 mmHg [VVS (○) and control (■)] A: positive correlation between \( C_{\text{calf}} \) at 20 mmHg [VVS (○) and control (■)] and \( \text{LTI} \). VVS demonstrated a generally lower \( C_{\text{calf}} \) and a reduced tolerance to LBNP. B: no correlation between \( V_{\text{cap}} \) response [VVS (○) and control (■)] and \( \text{LTI} \) \((r = 0.202, P = 0.30)\).
The VWM, which is based on physiological features of the venous vessel wall, was able to adopt the curvilinear form of the venous pressure-volume curve, and the overall adjustment to the experimentally induced pressure-volume curve was significantly better with the VWM than the QRE (Fig. 3, A–C). As expected, the major differences were found in the high pressure range, where the QRE was unable to model the curvilinear form of the pressure-volume curve. However, also in the low and intermediate ranges of the pressure-volume curve (15–40 mmHg), the VWM provided a lower mean deviance from the experimentally induced pressure-volume curve (Fig. 3C). Compared with the VWM, Ccalf was significantly underestimated in the high pressure range when calculated with the QRE (Fig. 3D).

In addition to studies on orthostatic intolerance, the applicability of the VWM extends over a broad spectrum. Several conditions in humans, e.g., diabetes mellitus, hypertension, and chronic venous insufficiency, as well as aging and sex differences, affect limb venous compliance (24, 36, 38, 40). Thus the ability of the VWM to characterize venous compliance over the entire pressure range may be of great importance for further understanding of physiological and pathophysiological aspects of venous function.

Calf Volume Changes

Excessive leg blood pooling in the upright position has been proposed to contribute to the symptoms in certain patients with orthostatic intolerance (50). Increased venous pooling has also been suggested by Hargreaves and Muir (18) as a potential cause of VVS, although their study is limited by the absence of a control group. In the present study no differences were found in Vcap between the groups. Independent from Vcap, net fluid filtration is an important contributor to lower limb volume load and, thus, an important aspect of the orthostatic reaction (30). However, we observed no differences in fluid filtration between VVS and control subjects during VOP. Our data are consistent with those reported by Stewart and Weldon (49) and suggest that the total volume load in the lower limb in the upright position is comparable in VVS and control subjects.

Although greater Ccalf and a concomitant increase in Vcap have been suggested to increase the vulnerability to orthostatic stress because of greater reductions in venous return and stroke volume (16, 28, 52), Ccalf has not been studied in a well-defined VVS population. We found Ccalf at high venous pressures to be comparable between the groups, also resulting in similar Vcap. However, Ccalf was significantly reduced in VVS at low transmural pressures (Fig. 4). This, is, nevertheless, consistent with earlier findings of Freeman et al. (8), who reported, contrary to their expectations, a lower Ccalf in patients with idiopathic orthostatic intolerance. They speculated that fluid shift from the vascular compartment to the interstitium during VOP could have affected their results. In the present study we corrected for the impact of net fluid filtration, and Ccalf was evaluated with the new VWM, which is able to produce a valid characterization of the whole pressure-volume and pressure-compliance relationship. Other factors, such as physical activity and sympathetic tone, could influence measurements of Ccalf (19, 33). However, there were no differences in physical activity levels between the groups, and prior studies investigating the role of sympathetic activation, via handgrip exercise and adrenergic blockade, found no direct effects on venous compliance (17, 43). Monahan and Ray (34) showed that venous compliance was unaltered in women during measurements at rest and LBNP (i.e., baroreceptor unloading). Other factors besides venous properties, such as a rigid fascia, could affect the pressure-volume curve during VOP, especially at high venous pressures. Nevertheless, in relation to the investigated pressure range, pressure transmission to underlying muscle tissue has been reported to be unchanged (80%) in young and older individuals (38). In view of this, we believe that our findings are valid.

Recent data from healthy individuals also suggest that the rate of limb blood pooling affects responses to orthostatic stress, where a faster institution of the hypovolemic stimulus is associated with greater sympathetic activation (21, 23). The stiffer venous vessels in VVS could lead to a slower blood pooling rate and attenuated sympathetic activation. Further studies are needed to address these questions in individuals with VVS.

LBNP Tolerance

LBNP induces central hypovolemia with concomitant unloading of baroreceptors and is a widely used technique to simulate and quantify orthostatic stress (2, 10, 23). As expected, LTI was lower in VVS than control subjects. There was a significant positive correlation between Ccalf measured in the low pressure range (20 mmHg) and LTI (Fig. 6A). However, no correlation was found between Ccalf in the higher pressure range and LTI, and, in analogy, we found no association between Vcap and LTI (Fig. 6B), further indicating that the functional elasticity of the veins at low transmural pressures, rather than the amount of pooled blood, is an important factor in the ability of an individual to withstand orthostatically induced stress. In contrast to the conventional view that a reduction in Ccalf may be beneficial in terms of orthostatic tolerance (16, 28, 52), we suggest that a high compliance at low venous pressures may be advantageous because of the inherent ability to mobilize substantial volumes of peripheral blood and concomitantly increase cardiac filling (42). Recent data also suggest reduced mobilization of peripheral blood in otherwise healthy women with low orthostatic tolerance (23).

In fact, this important first line of defense is initiated within seconds during acute hypovolemic stress (22, 25, 31, 41). Mobilization of peripheral venous blood is, to a major extent, a passive mechanism depending on two factors: 1) a decrease in transmural pressure over the venous wall as a result of resistance vessel constriction and 2) compliant venous walls (high venous compliance) facilitating passive recoil of blood to the heart (42, 46, 47). The strong association between the elasticity of the veins and the buffer function is also highlighted by the close relationship between Ccalf and Vcap (Fig. 5). Therefore, we reason that the reduced Ccalf at low venous pressures in VVS may adversely affect the compensatory mobilization of peripheral venous blood to the central circulation during hypovolemic stress and contribute to their hemodynamic instability. However, further clarification of the extent and impact of mobilization of capacitance blood on cardiovascular control in VVS is needed. Another aspect is whether stiffer venous vessels at low pressures in VVS could be involved in the modulation of stretch-mechanoreceptor gain.
and, thus, attenuate cardiopulmonary baroreceptor function. Lower cardiopulmonary baroreflex sensitivity has been demonstrated in VVS patients (51), although the result is not conclusive (45).

Limitations

First, the VWM cannot be used to evaluate the material properties within the venous vessel wall, i.e., elastin and collagen (1). Nevertheless, the main purpose of this study was to construct a valid model for the characterization of the entire venous pressure-volume relationship and, hence, the calculation of venous compliance. Second, we measured blood pooling in the lower limb, and differences in pooling in other vascular segments, e.g., the splanchnic circulation, cannot be excluded (48). Third, no women in the control group, but seven women in the VVS group, used contraceptives. Nevertheless, all women were investigated during the first 10 days of the follicular phase, i.e., with low concentrations of estrogen. Modern oral contraceptives usually mimic the normal menstrual cycle, and these women would also have low estrogen levels. Furthermore, C_{calf} seems to be unaffected by the use of contraceptives (26, 32). Fourth, previous reports point toward sex-specific differences in venous compliance and hemodynamic responses to LBNP, and women have lower tolerance of LBNP (4, 24, 26). Thus the present findings cannot be directly transferred to men. However, the greater prevalence of VVS in young women emphasizes the importance of studying women (12).

Perspectives and Significance

This study presents a new VWM that provides a valid characterization of the whole venous pressure-volume curve. The VWM may thus be a valuable tool in further studies of venous function. By using the VWM, we found that V_{cap}, as well as compliance, at high venous pressures was unaltered in women with VVS, indicating normal pooling of lower limb blood. However, C_{calf} at low venous pressures was significantly reduced in women with VVS and directly correlated to the impaired tolerance to hypovolemic stress. Reduced venous compliance at low venous pressures may adversely affect the compensatory mobilization of peripheral venous blood to the central circulation during hypovolemic circulatory stress and contribute to the orthostatic intolerance in women with VVS.

GRANTS

This work was supported by grants from Futurium-The Academy of Health Care, the Jönköping County Council, the Medical Research Council of South-east Sweden, and the Heart and Lung Foundation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.S., M.L., and H.Z. performed the experiments; J.S. analyzed the data; J.S., M.L., M.E., M.E., B.H., H.Z., and T.L. interpreted the results of the experiments; J.S. prepared the figures; J.S. drafted the manuscript; J.S., M.L., M.E., B.H., H.Z., and T.L. approved the final version of the manuscript; M.L., M.E., H.Z., and T.L. developed the concept and designed the research; M.L., M.E., B.H., H.Z., and T.L. edited and revised the manuscript.

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