Limb venous compliance in patients with idiopathic orthostatic intolerance and postural tachycardia

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Freeman, Roy, Vasilios Lirofonis, William B. Farquhar, and Marcelo Risk Limb venous compliance in patients with idiopathic orthostatic intolerance and postural tachycardia. J Appl Physiol 93: 636–644, 2002. First published April 5, 2002; 10.1152/japplphysiol.00817.2001.—Venous denervation and increased venous pooling may contribute to symptoms of orthostatic intolerance. We examined venous compliance in the calf and forearm in 11 orthostatic-intolerant patients and 15 age-matched controls over a range of pressures, during basal conditions and sympathetic excitation. Occlusion cuffs placed around the upper arm and thigh were inflated to 60 mmHg and deflated to 10 mmHg over 1 min. Limb volume was measured continuously with a mercury-in-Silastic strain gauge. Compliance was calculated as the numerical derivative of the pressure-volume curve.

The pressure-volume relationship in the upper and lower extremities in the basal and sympathetically activated state was significantly lower in the orthostatic-intolerant patients (all \( P < 0.05 \)). Sympathoexcitation lowered the pressure-volume relationship in the lower extremity in patients (\( P < 0.001 \)) and controls (\( P < 0.01 \)). Venous compliance was significantly less in patients in the lower extremity in the basal state over a range of pressures (\( P < 0.05 \)). Venous compliance was less in patients compared with controls in the upper (\( P < 0.005 \)) and lower extremities (\( P < 0.01 \)) in the sympathetically activated state, but there were no differences at individual pressure levels. Sympathetic activation did not change venous compliance in the upper and lower extremity in patients and controls. Patients with orthostatic intolerance have reduced venous compliance in the lower extremity. Reduced compliance may limit the dynamic response to orthostatic change and thereby contribute to symptoms of orthostatic intolerance in this population group.

venous occlusion plethysmography

PATIENTS DIAGNOSED WITH IDIOPATHIC ORTHOSTATIC INTOLERANCE REPORT SYMPTOMS OF LIGHTHEADEDNESS, FATIGUE, NAUSEA, PALPITATIONS, AND COGNITIVE IMPAIRMENT WHILE STANDING (22). THESE SYMPTOMS OCCUR IN THE PRESENCE OF A VIGOROUS TACHYCARDIA BUT GENERALLY IN THE ABSENCE OF SIGNIFICANT HYPOTENSION. THE PATHOPHYSIOLOGY OF THIS DISORDER IS NOT WELL UNDERSTOOD. PATHOPHYSIOLOGICAL MECHANISMS PROPOSED TO EXPLAIN THE TACHYCARDIA AND SYMPTOMS OF ORTHOSTATIC INTOLERANCE INCLUDE HYPOVOLEMIA (7), CARDIAC \( \beta \)-ADRENORECEPTOR SUPERSENSITIVITY, IMPAIRED CLEARANCE OF SYNAPTIC NOREPINEPHRINE (28), BAROREFLEX DYSFUNCTION (6), AND SELECTIVE SYMPATHETIC DENERVATION AFFECTING PROMINENTLY THE LOWER EXTREMITIES (12). STREETEN ET AL. (33, 34) SUGGESTED THAT LOWER EXTREMITY VENOUS DENERVATION WITH CONSEQUENT INCREASED VENOUS POOLING COULD CONTRIBUTE TO THE POSTURAL TACHYCARDIA AND SYMPTOMS OF ORTHOSTATIC INTOLERANCE IN THESE PATIENTS, THEREBY PROVIDING A POSSIBLE EXPLANATION FOR THE ASSOCIATION BETWEEN INCREASED VENOUS COMPLIANCE AND ORTHOSTATIC INTOLERANCE.

Several lines of evidence support the association between orthostatic intolerance and increased leg venous compliance. Convertino et al. (4) demonstrated that increased leg compliance was present in young healthy subjects after a 30-day exposure to 6° head-down bed rest. These conclusions are supported by others (3, 17, 18), although refuted by Melchior and Fortney (19) using bed-rest studies of shorter duration. Using standard techniques to assess calf venous compliance (4), our laboratory (6) previously reported, against expectations, that calf venous compliance was lower in patients with idiopathic orthostatic intolerance compared with a group of age-matched controls. We speculated, contrary to the hypothesis of Streeten et al. (33, 34), that increased sympathetic outflow to the venous system may have resulted in lower compliance (39). Alternately, we speculated that this finding might have been a consequence of the methodology employed to determine venous compliance; that is, because of incomplete venous drainage, patients were at a higher point on the pressure-volume curve when measurements were initiated. Therefore, the increase in calf volume from baseline (i.e., venous filling) was smaller, thus creating an impression of reduced venous compliance. If this is correct, the standard methodology of calculating a static estimate of compliance (4) may not be suitable for these patients. This interpretation appears to be supported by a report by Stewart and Weldon (32), which suggested that higher resting...

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venous pressure might give the appearance of a lower compliance in adolescents diagnosed with the postural tachycardia syndrome. In fact, when venous pressure was taken into account, there were no differences in compliance noted between those with orthostatic intolerance and controls.

To overcome the potential methodological limitations of assessing compliance at a single occlusive cuff pressure, we adopted the technique as outlined by Halliwill et al. (8). This method, a modification of the technique of Robinson and Wilson (23), allows the assessment of the pressure-volume relationship, over a range of pressures, during basal conditions and during a perturbation designed to increase sympathetic outflow. We hypothesized that venous compliance would be increased in patients with idiopathic orthostatic intolerance and that these alterations contribute to the pathophysiology of the disorder.

METHODS

Subjects. Eleven patients and fifteen control subjects agreed to participate in this institutionally approved study. Patients recruited for the study had idiopathic orthostatic intolerance defined by symptoms of orthostatic intolerance and an increase in heart rate of >30 beats/min within 10 min of an upright tilt without orthostatic hypotension. All patients also had chronic fatigue of >6 mo in duration. Medications were discontinued at least five half-lives before the study.

Assessment of venous compliance. The technique was adapted to assess the dynamic venous pressure-volume relationship of the arm and legs. Mercury-in-Silastic (D. E. Hokanson) strain gauges were placed around the midpoint of the right forearm and calf to measure change in limb volume. Both strain gauges were electronically calibrated before the protocol (10). An occlusion blood pressure cuff was placed around the upper arm and thigh (D. E. Hokanson). A rapid cuff inflator (model E-20, D. E. Hokanson) was used to inflate both cuffs simultaneously. The readout on the rapid cuff inflator was calibrated against a mercury sphygmomanometer. The arm and thigh blood pressure cuffs were inflated simultaneously to 60 mmHg and maintained for 4 min, while the change in limb volume was recorded. The pressure was then released over 1 min to 10 mmHg, with continuous measurement of cuff pressure and limb volume. The response of a representative subject is shown in Fig. 1. As the relationship between cuff pressure and venous pressure is less reliable <10 mmHg, these data were not used to generate the dynamic pressure-volume or compliance curves (8). The cuff pressure and limb volume were digitized and recorded at 500 Hz with WinDaq Data Acquisition Software (DATAQ Instruments).

Protocol. The subjects rested in the supine position with the arm and leg elevated above heart level for at least 15 min before instrumentation. Arm and leg limb filling and emptying were assessed during basal conditions and during a maneuver designed to increase sympathetic outflow. This was accomplished by inflating a blood pressure cuff on the opposite arm to 200 mmHg and having the subject perform ischemic, rhythmic handgrip exercise to fatigue for 2 min. Exercise was performed with the arm by using a spring-loaded handgrip device. The cuff remained inflated to 200 mmHg during the ramp down. Close attention was paid to ensure that no contraction occurred in the contralateral limbs. The basal measures and measures during sympathetic activation were performed in random order. All studies were performed with the arm and leg elevated slightly above heart level.

Peak oxygen consumption was determined in eight patients via open-circuit spirometry with a ParvoMedics TrueMax 2400 Metabolic Measurement System (Consentius Technologies, Sandy, UT) during cycling exercise to volitional

Fig. 1. Data from a representative subject showing the change in calf and forearm volume in response to inflation of a venous occlusion cuff to 60 mmHg and deflation to 10 mmHg over 1 min. A: cuff pressure. B: forearm volume. C: calf volume. Arrows, onset of cuff deflation after 4 min of venous filling.
fatigue on a Monark upright cycle. The protocol consisted of 2-min stages in which workload was increased by 25–30 W per stage. Subjects completed the College Alumnus Health Questionnaire (15) to assess weekly physical activity. Physical activities recorded on the questionnaire were classified according to energy expenditure (1).

Data analysis. During limb emptying, the individual pressure-volume relationships were quantitatively examined. The data recorded during each trial were averaged into 1-mmHg segments from 60 to 10 mmHg. The data were reduced to 50 pressure and volume data points. These data were used to generate pressure-volume curves. To avoid any a priori assumption on the pressure (P)-volume (V) relationship, compliance (C) was calculated as the numerical derivative of each pressure-volume data point pair with the following equation

\[ C_i = \frac{V_i - V_{i-1}}{P_i - P_{i-1}} \]

where \( 1 \leq i \leq 50 \)

This analytic method, which differs from that reported by Halliwill et al. (8), produces a more physiological compliance curve.

Statistics. The pressure-volume and compliance curves were analyzed with ANOVA. Separate analyses were done for the basal and sympathetic activated protocols in the upper and lower extremities. The dependent variable in the ANOVA model comparing the pressure-volume relationship in patients and controls was volume change, and the independent variables were main effect of level of pressure (10–60 mmHg) and main effect of group (patient or control) and their interaction. The dependent variable in the ANOVA model comparing the basal and sympathetic nervous system activated state in patients and controls was volume change, and the independent variables were main effect of level of pressure (10–60 mmHg) and main effect of group (patient or control) and their interaction. A similar model was used to compare compliance in patients and controls in the basal and sympathetically active state. The dependent variable in this model was compliance. The independent variables were the same. A \( P \) value of <0.05 was considered significant. If main effects or interactions were detected, subsequent post hoc analysis with Bonferroni correction was performed. Univariate correlation analyses were used to explore the relationship between measures of physical activity, level of physical fitness, and venous compliance. Values are reported as means ± SE.

RESULTS

Subject characteristics can be found in Table 1. All patients had orthostatic intolerance and chronic fatigue. Other symptoms in the patient group included recurrent muscle pain (64%), muscle weakness (64%), unrestful sleep (55%), sore throat (55%), inability to sleep (55%), and concentration difficulties (55%). There were no differences in age or body mass index between groups.

Pressure-volume relationships. There was a significant difference in the pressure-volume relationship between the orthostatic-intolerant and control groups in the upper and lower extremity in the basal and sympathetically activated state (all \( P < 0.05 \), ANOVA; see Fig. 2). Sympathetic activation significantly changed the pressure-volume relationship in the lower extremity in patients (\( P < 0.001 \), ANOVA; see Fig. 3) and controls (\( P < 0.01 \), ANOVA; see Fig. 3). Sympathoeexcitation did not change the pressure-volume relationship in the upper extremity. A comparison of the pressure-volume relationship in the upper extremity with that of the lower extremity was not significantly different in patients and controls in both the basal and sympathetically activated state (all \( P \) not significant, ANOVA; see Figs. 2 and 3).

Venous compliance. The venous compliance in the lower extremity was significantly less in the patients compared with the controls in the basal state (\( P < 0.05 \), ANOVA; see Fig. 4) and sympathetically activated state (\( P < 0.005 \), ANOVA; see Fig. 4). Post hoc analysis revealed significant differences between patients and controls in the basal state at 25, 30, 35, and 45 mmHg (\( P < 0.05 \)). Post hoc analysis of lower extremity compliance in the sympathetically activated state did not reveal significant between-group differences at individual pressures. The venous compliance in the upper extremity was significantly less in patients compared with controls in the basal and sympathetically activated states (\( P < 0.01 \), ANOVA; see Fig. 4). Post hoc analysis did not reveal significant between-group differences at individual pressures. Sympathetic activation did not change compliance in the upper or lower extremity in patients or controls (\( P \) not significant, ANOVA; see Fig. 5). There were no compliance differences between the upper and lower extremities.

Venous compliance, physical fitness, and level of physical activity. The peak \( O_2 \) uptake in the patients was 23.9 ± 2.4 ml·kg\(^{-1}\)·min\(^{-1}\). The physical activity level in the patients was 1,110.8 ± 252.3 vs. 7,602.9 ± 1,374.6 kcal/wk in controls (\( P < 0.01 \)). There were no significant correlations between venous compliance and levels of physical fitness or physical activity in the orthostatic-intolerant patients (see Table 2). Correlations at most pressure levels suggested an inverse relationship between venous compliance and levels of physical fitness and physical activity: the fitter patients and more physically active patients had lower venous compliance. There were no significant correlations between amount of physical activity and venous compliance in the controls.

DISCUSSION

The major findings of this study are as follows: 1) venous compliance in the basal state was significantly lower in the lower extremity of orthostatic-intolerant patients compared with controls across a range of pres-
sures; this difference was not present in the upper extremity (see Fig. 4, A and C); 2) although venous compliance was lower in patients compared with controls in the sympathetically activated state, there were no differences between the groups at individual pressure levels (see Fig. 4, B and D); 3) sympathetic activation did not change venous compliance in the upper and lower extremity in patients and controls (see Fig. 5); and 4) venous compliance was similar in the upper and lower extremity.

Postural tachycardia is a common cause of orthostatic intolerance (22). The pathophysiological basis of this disorder is unknown. As in the present cohort, there is a strong association with chronic fatigue (25). Several lines of evidence support the association of the postural tachycardia with partial sympathetic denervation that predominantly affects the lower extremities. Such evidence includes the presence of excessive venous pooling in the lower extremities (35) accompanied by hypersensitivity to an infusion of norepinephrine in the veins of the foot, suggesting impaired sympathetic innervation of foot veins (33, 34), prolonged latency of the sympathetic skin response (peripheral autonomic surface potential) in the lower extremity (9), more pronounced impairment of sweating in the legs than the arms (26), supersensitivity to the $\alpha$-adrenoceptor agonist phenylephrine (13), and a relative decrease in norepinephrine spillover in the lower extremities (12).

Based on this evidence, one might anticipate increased leg venous compliance and excessive blood pooling in the lower extremities of patients with postural tachycardia. Indeed, Streeten (33, 34) and others (26) have proposed that excessive pooling of blood in the legs as a result of abnormal compliance may be a potential mechanism responsible for symptoms of orthostatic intolerance in selected patients. This assertion receives strong support from simulated microgravity studies in which most reports have documented increased leg compliance after head-down bed rest of varying duration (3, 4, 17, 18) and associated with reductions in calf muscle mass (4). Although a recent report failed to demonstrate an increase in venous compliance after short-duration (4–12 days) spaceflight (38), consistent with the short-duration bed-rest studies of Melchior and Fortney (19), based on the majority of studies, one might anticipate that the deconditioning associated with orthostatic intolerance and the ensuing loss of muscle mass would further increase venous compliance. Our laboratory (6), therefore, previously hypothesized that leg compliance would be increased in patients with orthostatic intolerance, and we were surprised to find that venous compliance was lower in patients than controls.

The present data, with the use of a slightly higher cuff pressure and a dynamic limb-emptying protocol, were consistent with the data obtained by using the single-step method (6). The average compliance of the
patients across the range of pressures was 78% that of the controls compared with 68% with the use of the single-step method. Several mechanisms may be responsible for our findings. First, the difference in compliance could be explained by fluid shifts from the microvasculature to the interstitium. This has been reported in individuals with diabetes, where it is thought to be related to increased microvascular permeability (11). Increased microvascular filtration with ensuing increased interstitial fluid could alter tissue properties and lead to the observed changes in the pressure-volume relationship. Brown and Hainsworth (2), using impedance plethysmography, suggested that patients with orthostatic intolerance had increased capillary filtration in the legs. Similar conclusions were drawn by Stewart and Weldon (30) using mercury-in-Silastic venous occlusion plethysmography. It is thus possible that increased microvascular filtration may, in part, explain not only compliance differences but also the reduction in plasma volume observed in some patients, particularly if the deficit is more widespread and extends to the splanchnic and other vascular beds (36).

Second, it is possible that the compliance differences may be a consequence of structural remodeling of the vasculature and/or supporting tissues. Several authors have observed structural and functional changes in the microvasculature in animal models of microgravity (5, 27). Human studies lend additional support to these observations. A recent report by Monahan et al. (20) documented lower venous compliance in sedentary young and older subjects. Lawler et al. (14) reported a cross-sectional study of healthy volunteers that showed no relationship between leg muscle mass and lower body negative pressure tolerance. Based on these results, they suggested that chronic loss of muscle mass may lead to compensatory changes in the fascia and other supporting tissues. It is possible that similar changes exist in patients with orthostatic intolerance, although our cross-sectional study does not support a relationship among levels of physical fitness, physical activity, and venous compliance. The role of chronic deconditioning and reduced venous compliance in this population could be explored more satisfactorily in a longitudinal study with an exercise intervention.

We hypothesized that the observed decrease in venous compliance might be a homeostatic mechanism, mediated by the sympathetic nervous system, to minimize venous pooling and thereby increase central blood volume in these individuals with orthostatic intolerance. Were this the case, we would anticipate that sympathetic activation in control subjects would yield a compliance curve that is similar to that obtained in the orthostatic-intolerant subjects. The present data lend limited support to that hypothesis. Our data, consistent with those of others using the same technique but a different analytic method (8), fail to show a significant difference in venous compliance between
the basal and sympathetically activated states. Sympathoexcitation did, however, result in lower volumes in the lower extremities in patients and controls (see Fig. 3) and an insignificant trend toward decreased compliance in the calves of controls (see Fig. 5).

This observation is surprising, given the role of the sympathetic nervous system in the acute maintenance of cardiovascular homeostasis in response to orthostatic change. However, because sympathetic outflow to vascular beds does not occur in parallel, it is possible that muscle chemoreflex activation is not the appropriate provocative stimulus to enhance sympathetic outflow to the venous system. Furthermore, whereas it is well established that the sympathetic nervous system innervates the venous system (16, 33), the functional role of this innervation in the maintenance of orthostatic tolerance is not firmly established, and it is likely that the skeletal muscle pump plays a greater role in the maintenance of orthostatic tolerance (29).

We did not find a difference between the upper and lower extremity venous compliance. This finding is surprising, as one might anticipate that there would be reduced venous compliance in the dependent venous system to minimize venous pooling in response to the increase in lower extremity hydrostatic pressures generated on the assumption of the upright posture. Prior reports addressing this issue are conflicting, with some studies reporting increased (37) and others decreased (8) compliance in the upper hemibody.

The changes in the pressure-volume relationship may have pathophysiological consequences in patients with orthostatic intolerance. Rowell observed that the shape of the venous pressure-volume curve is a “compromise in design” (24). In normal subjects, venous compliance is high at low pressures and low at high pressures. The flat portion of the curve prevents excessive gravity-induced venous pooling in the dependent circulation when upright, thereby allowing bipedal humans to maintain adequate central blood volume while standing. The steep portion of the curve, while predisposing humans to orthostatic intolerance, allows for large changes in volume with only small changes in pressure. This characteristic enables the venous system to buffer rapid decreases in central blood volume to maintain cardiovascular homeostasis. In orthostatic-intolerant subjects, the flat portion of the curve is shifted downward, and the steep portion is flattened. This change has two possible consequences. The downward shift of the flat portion of the curve may be an adaptive change that improves orthostatic tolerance. The flattening of the steep portion, however, may reduce the dynamic buffering of transient volume shifts and may, as suggested by Olsen and Lanne (21) in their report of reduced venous compliance in the elderly,
impair the response to circulatory stress in this patient group. It remains uncertain as to which of these effects dominates and the extent to which these observations contribute to the symptoms of orthostatic intolerance.

A limitation of our study is that we have no direct measure of venous pressure. We cannot be sure that basal venous pressures were equivalent in the two subject groups. Halliwill et al. (8) suggested that cuff pressure is an acceptable surrogate measure of venous pressure between 10 and 60 mmHg. This relationship, however, may not apply to the patient group. Whereas venous occlusion pressure may approximate venous pressure, even in normal subjects, resting venous pressure was not zero. This difference may be greater in patients. Stewart and Weldon (30, 31) have suggested that basal venous pressure is higher in adolescents with postural tachycardia, giving the appearance of lower compliance. When measured relative to a calculated resting venous pressure, the difference in compliance was no longer apparent. However, Stewart and Weldon (31), in a follow-up study using a different technique, demonstrated a trend toward reduced distensibility and capacitance only across the 10- to 30-mmHg range. These results are more consistent with the present data. Nevertheless, this question remains uncertain in the absence of direct measures of venous pressure, particularly given the nonlinearities in the pressure-volume relationship. Direct measurement of venous pressure should be considered in future studies. An additional limitation of our study is the absence of an index of sympathetic activation. Care was taken to ensure adequate effort by both patients and controls; however, we are not able to quantify the magnitude of sympathoexcitation in either population. Finally, whereas we paid close attention to ensure that limb muscle tensing did not occur during compliance assessments, we cannot exclude this possibility.

In summary, our data show that the pressure-volume characteristics for patients differ from those of controls. In essence, isobaric analysis of the pressure-volume curves reveals that the volume difference at a

<table>
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<tr>
<th>Pressure, mmHg</th>
<th>Peak VO₂, ml·kg⁻¹·min⁻¹</th>
<th>Physical Activity, kcal/wk</th>
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</thead>
<tbody>
<tr>
<td>15</td>
<td>0.06</td>
<td>-0.19</td>
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<tr>
<td>20</td>
<td>-0.37</td>
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<td>25</td>
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<tr>
<td>30</td>
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<td>-0.54</td>
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<tr>
<td>40</td>
<td>-0.38</td>
<td>0.25</td>
</tr>
<tr>
<td>45</td>
<td>-0.38</td>
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</tr>
<tr>
<td>60</td>
<td>0.15</td>
<td>0.12</td>
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VO₂, O₂ uptake.
given pressure is greater in controls in both the upper and lower extremities and that compliance in the lower extremity is reduced in the patients relative to the controls. Furthermore, our data show that sympathetic nervous system activation does not alter venous compliance in either patients or controls. The pathophysiological significance of this finding is unknown. Whereas it is unlikely that reduced venous compliance is the primary cause of orthostatic intolerance, it may compound the pathophysiological abnormalities of that disorder. The venous system may be viewed as a capacitor that permits a dynamic response to orthostatic change. Viewed from this perspective, the reduced venous compliance observed in the orthostatic-intolerant subjects may paradoxically further limit the extent of the response to orthostatic stress and may contribute to symptoms of orthostatic intolerance in this population group.

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REFERENCES


35. Streeter DH, Anderson GH Jr, Richardson R, and Thomas FD. Abnormal orthostatic changes in blood pressure and heart


