Cardiac homeostasis is independent of calf venous compliance in subjects with paraplegia

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Cardiac homeostasis is independent of calf venous compliance in subjects with paraplegia. Am J Physiol Heart Circ Physiol 284: H2393–H2399, 2003. First published February 27, 2003; 10.1152/ajpheart.01115.2002.—The purpose of this study was to examine cardiac hemodynamics during acute head-up tilt (HUT) and calf venous function during acute head-down tilt (HDT) in subjects with paraplegia compared with sedentary nondisabled controls. Nineteen paraplegic males (below T6) and nine age-, height-, and weight-matched control subjects participated. Heart rate, stroke volume, and cardiac output were assessed using the noninvasive acetylene uptake method. Venous vascular function of the calf was assessed using venous occlusion plethysmography. After supine measurements were collected, the table was moved to 10° HDT followed by the three levels of HUT (10, 35, and 75°) in random order. Cardiac hemodynamics were similar between the groups at all positions. Calf circumference was significantly reduced in the paraplegic group compared with the control group (P < 0.001). Venous capacitance and compliance were significantly reduced in the paraplegic compared with control group at supine and HDT. Neither venous capacitance (P = 0.37) nor compliance (P = 0.19) increased from supine with 10° HDT in the paraplegic group. A significant linear relationship was established between supine venous compliance and supine cardiac output in the control group (r = 0.80, P < 0.02) but not in the paraplegic group. The findings of reduced calf circumference and similar venous capacitance at supine rest and 10° HDT in the paraplegic group imply that structural changes may have limited venous dispensability in individuals with chronic paraplegia. Furthermore, the lack of a relationship between supine venous compliance and supine cardiac output suggests that cardiac homeostasis does not rely on venous compliance in subjects with paraplegia.

spinal cord injury; head-up tilt; venous capacitance; skeletal muscle mass atrophy

DURING ACUTE GRAVITATIONAL STRESS, adequate venous tone is a major contributor to cardiac preload and can provide a rapid compensation of blood volume from the lower extremities to the central cavity, thereby maintaining venous return and cardiac output (CO) (1, 2, 27). Increases in venous tone are controlled by the autonomic nervous system via sympathetic vasomotor tone and an active skeletal muscle pump. In individuals with paraplegia, sympathetic denervation of the lower extremity and an inactive or diminished skeletal muscle pump may contribute to an inability to adequately redistribute blood volume during orthostasis (17).

In nondisabled persons, the deep veins of the lower extremity contain a large portion of the total venous volume, are poorly innervated by the sympathetic nervous system, and lack vascular smooth muscle (6). These deep veins rely on the surrounding skeletal musculature to maintain adequate blood volume distribution during gravitational stress. There is evidence to suggest that skeletal muscle atrophy is associated with increased lower extremity blood pooling during orthostasis in nondisabled humans (5, 24, 34). Furthermore, limited venous distension and subsequent blood pooling during orthostasis have been associated with reduced leg compliance and increased calf muscle mass (7, 8). Because of paralysis and the associated disuse, lower extremity lean tissue is lost at a rate of ~13 g/day during the first year after a traumatic spinal cord injury (39). Furthermore, total body lean tissue continues to decline at an accelerated rate in persons with spinal cord injury (4%/decade) compared with nondisabled controls (2%/decade) (31).

These concomitant problems facing individuals with paraplegia suggest that they would be highly susceptible to orthostatic intolerance. Despite significant reductions in muscle mass and sympathetic activity of the lower extremity, resting and orthostatic cardiac hemodynamics, i.e., CO, stroke volume, and heart rate, have been reported as similar in persons with paraplegia and nondisabled controls (11, 12, 18, 20, 38). It is unclear how central hemodynamics are maintained during gravitational stress in persons with lower ex-
tremity denervation and skeletal muscle atrophy. A possible explanation is an intact vеноarteriolar reflex, and there is evidence to suggest that this reflex is intact in persons with paraplegia (33). The normal cardiac hemodynamics documented in persons with paraplegia may also be driven by morphological changes within the calf, which serve to limit venous blood pooling during orthostasis (16, 37).

The purpose of this study was to examine cardiac hemodynamics while in the supine position and during acute head-up tilt (HUT) in persons with paraplegia compared with sedentary nondisabled controls. A second purpose was to measure calf venous capacitance (VVV) and venous compliance (VC) at supine rest compared with acute head-down tilt (HDT) in subjects with chronic paraplegia and to identify a relationship between supine VC and supine CO.

METHODS

Subjects. All subjects (n = 28) were sedentary males between the ages of 27 and 53 yr who had not participated in any form of regular physical activity for at least 6 mo before the investigation, as assessed by questionnaire. Subjects were without known cardiovascular or pulmonary diseases or diabetes mellitus, and all were current nonsmokers for a minimum of 1 yr before the investigation. Subjects with paraplegia (n = 19) were healthy outpatients, with a minimum of 2 yr postinjury, and capable of maintaining an independent lifestyle. With the use of the American Spinal Injury Association (ASIA) classification of neurological impairment, 9 individuals were diagnosed with a complete injury (47%: ASIA A) and the other 10 individuals were diagnosed with an incomplete injury (53%: ASIA B and C). Individuals with paraplegia were also classified according to their postural habits; a survey was used to determine the frequency and duration with which they assumed a standing upright posture using assistive devices. The control subjects (n = 9) were matched for age, height, and weight to the subjects with paraplegia. The Institutional Review Board for Human Studies of the Bronx Veterans Affairs Medical Center granted approval for the study, and informed consent was obtained before the investigation.

Protocol procedures. Subjects reported to the laboratory between 10 AM and 1 PM, were at least 3 h postprandial, and had refrained from caffeine and heavy exertion for a minimum of 24 h before being tested. Upon arrival to the laboratory, subjects were instructed to lie on a tilt table, where supine lung volumes and the diffusion capacity of carbon monoxide at the lung were assessed with a Vmax system (V229D) equipped with diffusion software (SensorMedics; Yorba Linda, CA) (19). While the subjects rested quietly, ECG electrodes, occlusion plethysmography cuffs, and the strain gauge were applied. After 20 min of rest in a thermonutral environment (21–23°C), supine measurements were collected.

Tilt table testing. After baseline testing was performed, the tilt table was adjusted to the 10° HDT position, and all cardiac and venous measures were collected. The table was returned to the horizontal position, and the subjects were instructed to reposition themselves for the three HUT positions (10, 35, and 75°), which were performed in random order. These three specified HUT positions were chosen because of the linear gradation in orthostatic pressure produced by the sine of these angles at the chest (i.e., 0.17, 0.57, and 0.97 Gz). The adjustment of the tilt table took <10 s to attain each of the specified positions, and all measurements were made within 3 min, thus constituting the acute phase of an orthostatic provocation.

Noninvasive CO. The method used in this investigation assumes that blood flow to the lungs is equal to blood flow to the heart. The concentration of expired acetylene during a constant-rate exhalation maneuver relative to methane, which is not absorbed, and carbon monoxide, which is readily absorbed, is used to calculate pulmonary capillary blood flow (9, 19, 28). CO is then calculated from the pulmonary capillary blood flow and expiratory flow rate plus physiological shunt (26). Zenger and co-workers (42) reported a correlation coefficient of 0.90 with a slope of 0.98 comparing noninvasive CO with thermodilution. The noninvasive CO maneuver requires exhalation to reserve volume, test gas inhalation to 90% vital capacity, and then a constant-rate exhalation back to reserve volume (42). The constant-rate exhalation maneuver was maintained with a resistive flow device in the mouthpiece, coaching from the investigator, and a visual cue on the monitor. This maneuver was repeated at supine rest and within 3 min of positioning the subject at 10° HDT and 10, 35, and 75° HUT.

Venous occlusion plethysmography. Data were collected at supine rest and at 10° HDT. While in the supine position, the left leg was supported at the ankle 10 in. above horizontal to allow for venous emptying. Maximal calf circumference was determined for strain-gauge placement and as an indicator of calf muscle mass. Two pressure cuffs were placed on the leg, one at midthigh and one distal to the calf at the ankle. While the ankle cuff was inflated to a suprasystolic pressure (160–180 mmHg), venous occlusion was performed by rapidly inflating the thigh cuff (within 2 s) to a pressure 5 mmHg below diastole [displayed on a beat-to-beat basis by a Finapres (Ohmeda)]. The mercury-in-rubber strain gauge (Hokanson, Bellevue, WA) detected the change in limb volume from 60 s of unimpeded arterial inflow while venous outflow was occluded (40). Sixty seconds of occlusion pressure were chosen to illuminate changes within the venous vasculature with minimal occurrence of capillary filtration (36). All measurements were determined based on a calibration spike, marked 5 s before cuff inflation, representing a change in voltage equal to a 1% change in limb volume (4). VVV was assessed as the percent change in limb volume from the start of the occlusion cycle to the peak change obtained in 60 s of occlusion. VC was calculated as the volume change at peak occlusion (VVV) divided by cuff pressure using the following formula: VV VOCCLUSION pressure (in mmHg) × 100 (10, 40). Additionally, arterial inflow (%change/s) was estimated as the first derivative of the inflow curve taken at 0.5 s after the start of cuff occlusion, corresponding to the linear phase of the inflow curve (40).

Heart rate and blood pressure. Heart rate was continuously monitored during the testing using a three-lead configuration by a 742 Mennen Medical ECG Monitor (Bio-Medical Equipment Service; Louisville, KY) with the recording electrode placed at the V5 position. Blood pressure was measured continuously from a photoplethysmographic (Finapres, Ohmeda), which was attached to the middle phalanx of the middle finger with the arm supported horizontally at the height of the right atrium.

Data analysis. All continuous variables are reported as means ± SD. The venous occlusion curves were analyzed using a customized program created with LabView program-
CARDIAC OUTPUT AND VENOUS COMPLIANCE IN SUBJECTS WITH PARAPLEGIA

Table 1. Subject characteristics

<table>
<thead>
<tr>
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<th>Paraplegia</th>
<th>Control</th>
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<tr>
<td>n</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>39 ± 9</td>
<td>39 ± 7</td>
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<tr>
<td>Height, cm</td>
<td>179 ± 8</td>
<td>174 ± 9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85 ± 22</td>
<td>80 ± 8</td>
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<td>Body mass index, kg/m²</td>
<td>26.3 ± 5.8</td>
<td>26.6 ± 2.2</td>
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<tr>
<td>Body surface area, m²</td>
<td>2.03 ± 0.26</td>
<td>1.95 ± 0.13</td>
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<tr>
<td>Calf circumference, cm</td>
<td>31.0 ± 4.5</td>
<td>37.5 ± 2.0*</td>
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<tr>
<td>Duration of injury, yr</td>
<td>11 ± 7</td>
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Data are presented as means ± SD; n, no. of subjects. *Significant group comparison, P < 0.001.

Results

Subject demographic characteristics are presented in Table 1; there were no differences between the groups for any demographic parameter other than calf circumference, which was significantly reduced in the group with paraplegia compared with the controls (p < 0.001). Regardless of completeness of injury or postural habits, cardiac hemodynamics, VVV, and VC were not significantly different at the supine position or at any degree of orthostasis among the individuals with paraplegia. Thus, in our analysis of the results, subjects with paraplegia are reported as a single group.

Cardiac hemodynamic data are displayed in Fig. 1. A significant main effect for tilt angle was evident in both groups for cardiac hemodynamics (heart rate: P < 0.0001; stroke volume: P < 0.0001; CO: P < 0.01). Furthermore, the change in cardiac hemodynamics across tilt angle was similar between the groups. Heart rate rose from the supine to 75° HUT position in both groups (paraplegia: 17 ± 10 beats/min, range: 5–41 beats/min; control: 17 ± 9 beats/min, range: 3–32 beats/min), whereas stroke volume was reduced across tilt angles (paraplegia: 17 ± 21 ml/beat, range: 12–80 ml/beat; control: 21 ± 14 ml/beat, range: 3–83 ml/beat). CO was significantly reduced with progressive acute HUT from the supine position to 75° tilt by 32% in the paraplegic group (1.7 ± 2.1 l/min, P < 0.01) and by 38% in the control group (2.1 ± 1.4 l/min, P < 0.01).

A typical venous occlusion graph is presented in Fig. 2, demonstrating a characteristic subject from each group for the venous occlusion maneuver. There was no significant difference in supine arterial inflow between the paraplegic and control groups (4.3 ± 2.6 vs. 5.5 ± 4.6% change/s, P = 0.50, respectively). Group mean differences are depicted for VVV and VC at the supine and 10° HDT positions in the group with paraplegia and controls in Fig. 3. There was no significant increase in VVV (P = 0.37) or VC (P = 0.19) with HDT compared with supine values in the group with paraplegia. Likewise, in the control group, VVV (P = 0.51) was unchanged from the supine position with 10° HDT; however, increases in VC with the HDT maneuver approached significance (P = 0.06). Furthermore, at both positions, VVV (P < 0.0001) and VC (P < 0.0001) were significantly reduced in the group with paraplegia compared with controls.

The relationship between supine CO and supine VC was significant in the control group (r = 0.80, P < 0.02); no such relationship was noted in the group with paraplegia (Fig. 4).

Discussion

This report examined cardiac hemodynamics, VVV, and VC of the calf while in the supine position and during orthostatic provocations in persons with paraplegia and in sedentary nondisabled controls. Cardiac
hemodynamics were similar between the groups at supine rest and during acute HDT and HUT, as previously reported (12, 18, 20, 38). CO during passive tilting is maintained by increases in heart rate, which are compensatory to losses in central filling pressure, venous return, and reduced stroke volume (13). Comparable findings in the groups tested herein suggest that intravascular volume redistribution was adequate for the maintenance of cardiac homeostasis during acute HUT in individuals with paraplegia. Houtman and colleagues (18) reported similar findings and postulated that venous vascular atrophy below the level of lesion might simply limit blood pooling during HUT and thus contribute to the maintenance of cardiovascular homeostasis.

Venous atrophy has been previously reported in subjects with paraplegia at rest and during arm-crank exercise (16, 17), whereas others have suggested that during upper extremity exercise, the leg vasculature acts as a reservoir for significant blood pooling (21, 29). We previously speculated (37) that if venous blood pooling occurred during seated occlusion plethysmography, the veins would be distended before the maneuver, thereby reducing capacitance potential after the maneuver. This speculation was in accordance with previous reports of increased deep vein blood pooling with lower extremity atrophy due to reduced surrounding skeletal muscular support (6, 7). To test this hypothesis, subjects were positioned at 10° HDT in an attempt to empty the veins more completely. If venous blood pooling occurs in subjects with paraplegia, this maneuver should increase measurable VC at 10° HDT compared with the supine position. However, VC did not increase from supine to 10° HDT in the group with paraplegia, and was significantly reduced at both positions compared with the control group. Group differences in arterial inflow could account for the reduction in VC reported in the group with paraplegia. With the use of the venous occlusion curves (Fig. 2), we found no statistical difference in arterial inflow between the two groups, and the vessel reached peak distention more rapidly in the group with paraplegia (<10 s) than in the control group (at 50 s). Furthermore, given that the occlusion maneuver was held for only a period of 60 s, it is unlikely that blood volume was lost to the extravascular space in either group (36), emphasizing that the differences reported between the groups most likely reflect changes within the venous vasculature. Therefore, assuming similar blood volume between the groups, the implication is that VC is reduced in sub-

Fig. 2. A typical supine venous occlusion graph for a representative sedentary control subject (A) and a subject with paraplegia (B). The dashed line represents the calibration spike or the voltage equivalent to a 1% change in limb volume.

Fig. 3. Mean venous capacitance (A) and venous compliance (B) at the supine and 10° head-down tilt (HDT) positions in subjects with paraplegia and sedentary controls. *P < 0.01 and **P < 0.001, paraplegia vs. control.
The association between skeletal muscle mass and leg compliance has been addressed by several investigators. In a cross-sectional investigation, Convertino et al. (7) reported an inverse relationship between skeletal muscle mass of the calf (computed tomography) and leg compliance (venous occlusion plethysmography). Similarly, longitudinal investigations have reported significant reductions in calf muscle cross-sectional area after prolonged exposure to simulated microgravity (HDT) in association with increased leg compliance (5, 8). On the other hand, calf skeletal muscle hypertrophy from chronic resistance exercise training has been reported to reduce leg compliance (23, 32). Lawler et al. (22) tested the hypothesis that subjects with less leg muscle (dual energy X-ray absorptiometry) would have increased venous blood pooling during lower body negative pressure (LBNP) and an increased propensity toward orthostatic intolerance (22). These authors reported no association between lower extremity lean tissue and orthostatic tolerance and concluded that alterations in muscle mass that were not associated with specific interventions, such as bed rest or resistance training, did not predict a response to LBNP (22). The specific effect of chronic spinal cord injury on the relationship among lower extremity muscle, leg compliance, and orthostatic tolerance has not been thoroughly investigated, and the report herein is a preliminary view of these complex associations.

Calf VC was investigated during various degrees of HUT in nondisabled subjects, and it was determined that calf compliance measured during HUT equals supine compliance because factors known to affect compliance, i.e., calf muscle activation (<10% maximal voluntary), are ineffectual in producing volume change during supported orthostasis (35). During orthostasis, pressure in the leg vasculature is increased, and a more compliant vessel will have a greater capacity for volume expansion, thereby potentially reducing central filling pressures at the atrium. Previously, vascular compliance of the common femoral artery was reported as 42% lower in subjects with paraplegia compared with sedentary nondisabled control subjects (30). In the current study, supine VC was ~72% lower in the group with paraplegia compared with the sedentary controls and 90% lower at 10° HDT. Although calf VC was significantly reduced in the group with paraplegia, cardiac hemodynamics during acute HUT were comparable in the control group. The relationship between supine VC and CO was determined in the current study; a significant association was established in the control group (r = 0.80, P < 0.02), whereas no relationship was found in the group with paraplegia. It may be implied from our findings that, in persons with paraplegia, calf VC is not a critical mechanism by which central intravascular volume and cardiac homeostasis are maintained. Structural changes within the calf muscle sarcomere arrangement might be responsible for this finding.

The significantly reduced calf circumference in the group with paraplegia compared with the controls reported herein, although not exclusive, is thought to represent muscle atrophy due to disuse associated with paraparesis (31, 39). With the use of dual energy X-ray absorptiometry, we (39) recently observed the rate of change in lean tissue mass during the first year after traumatic spinal cord injury. The results of this investigation demonstrate that the loss of lean tissue over the first 12 mo was most dramatic in the lower extremity, averaging 3.1 kg in individuals with paraplegia. In a study of monozygotic twins discordant for spinal cord injury, our laboratory (31) has reported that the injured twin had, on average, a 10-kg loss in lower extremity lean tissue compared with his/her twin, and the duration of injury was significantly correlated with total body lean tissue, suggesting that lean tissue loss continues throughout the chronic phase of the injury. Although calf circumference is a crude measure of body composition, on the basis of these previous reports, we feel that the significantly reduced calf circumference in the group with paraplegia most likely reflects skeletal muscle atrophy; however, a more extensive look into lower extremity body composition and venous vascular function is necessary to fully describe these associations.
venous vasculature and skeletal muscle atrophy may simply limit blood pooling during acute HUT and help to maintain central blood volume in persons with low-level paraplegia (18). This conclusion is in opposition to previous reports of lower extremity skeletal muscle atrophy and associated increased leg compliance and therefore deserves further examination of the possible muscular and vascular structural changes that occur with disuse atrophy and paralysis.

Factors other than the properties of the veins may effect VC, including stiffening of the vasculature and a rigid surrounding fascia, which may limit distension during volume expansion maneuvers. An increase in the collagen-to-elastin ratio (3), as well as a venous wall thickening comparable to the known arterial wall thickening that occurs with age (14), may play a role in the reduced capacitance reported in the group with paraplegia. Restriction of the muscle fascia envelope was associated reduced limb compliance in an aged population (25) and may be an alternative explanation to the current findings. We did not investigate the histochemistry or morphology of the surrounding tissue or of the veins and can therefore only speculate that structural changes within the calf may have contributed to the findings reported herein. The pathophysiologic significance of reduced VC in persons with paraplegia is currently unknown; however, blood volume distribution has been shifted such that central volume is maintained during orthostasis. In the aged population, reduced compliance in response to LBNP was associated with a relatively fixed central blood volume and a deactivation of the baroreceptors (25). These results may also apply to populations with spinal cord injury.

Another possible contribution to the maintenance of central cardiac function reported in the group with paraplegia is the activation of the vеноarteriolar reflex, which has been reported to contribute ~45% to the change in vascular tone with upright posture (15) in healthy nondisabled controls. In subjects with paraplegia, an exaggerated reduction in cutaneous vascular conductance of the ankle and foot compared with controls was documented during lower leg dependency (33). This observation supports the existence of the vеноarteriolar reflex in persons with paraplegia, which may contribute to cardiovascular stability during orthostasis.

In conclusion, the maintenance of cardiac homeostasis during acute orthostatic provocation in subjects with paraplegia does not seem to be dependent on calf VC. Possible skeletal muscle and venous vascular morphologic changes may limit blood pooling during orthostasis in persons with paraplegia and contribute to central volume maintenance. The implications of a limited blood pool reservoir in the lower extremity may lead to impaired baroreceptor function and an increased risk of hypertension, which has been reported in this population (41).

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