Smaller age-associated reductions in leg venous compliance in endurance exercise-trained men

KEVIN D. MONAHA N,1 FRANK A. DINENNO,1 DOUGLAS R. SEALS,1,2 AND JOHN R. HALLIWILL3
1Human Cardiovascular Research Laboratory, Center for Physical Activity, Disease Prevention, and Aging, Department of Kinesiology and Applied Physiology, University of Colorado at Boulder, Boulder, Colorado 80309; 2Divisions of Cardiology and Geriatric Medicine, Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262; and 3Department of Anesthesiology, Mayo Clinic and Foundation, Rochester, Minnesota 55905

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Monahan, Kevin D., Frank A. Dinenna, Douglas R. Seals, and John R. Halliwill. Smaller age-associated reductions in leg venous compliance in endurance exercise-trained men. Am J Physiol Heart Circ Physiol 281: H1267–H1273, 2001.—We determined the independent and interactive influences of aging and habitual endurance exercise on calf venous compliance in humans. We tested the hypotheses that calf venous compliance is 1) reduced with age in sedentary and endurance-trained men, and 2) elevated in young and older endurance-trained compared with age-matched sedentary men. We studied 8 young (28 ± 1 yr) and 8 older (65 ± 1) sedentary, and 8 young (27 ± 1) and 8 older (63 ± 2) endurance-trained men. Calf venous compliance was measured in supine subjects by inflating a venous collecting cuff, placed above the knee, to 60 mmHg for 8 min and then decreasing cuff pressure at 1 mmHg/s to 0 mmHg. Calf venous compliance was determined using the first derivative of the pressure-volume relation during cuff pressure reduction (compliance = β1 + 2-β2-cuff pressure). Calf venous compliance was reduced with age in sedentary (~40%) and endurance-trained men (~20%) (both P < 0.01). Furthermore, calf venous compliance was ~70–120% greater in endurance-trained compared with age-matched sedentary men and ~30% greater in older endurance-trained compared with young sedentary men (both P < 0.01). These data indicate that calf venous compliance is reduced with age in sedentary and endurance-trained men, but compliance is better preserved in endurance-trained men.

ORTHOSTATIC STRESS promotes translocation of thoracic blood volume into the compliant venous system of the legs, buttoc k, and pelvis in humans (1, 28). This rapid inferior fluid shift reduces central blood volume and cardiac preload, transiently compromises arterial blood pressure, and represents a substantial cardiovascular stress as reflected in reflex increases in heart rate and sympathetic nerve activity (3). In humans, these responses can be markedly reduced if fluid shifts into the legs are prevented (17), indicating that the compliance of the leg veins is a critically important variable in determining the cardiovascular stress incurred as a result of orthostasis. Therefore, factors affecting leg venous compliance appear to be important in the context of orthostatic tolerance.

Aging and habitual endurance exercise are two chronic physiological states that may influence leg venous compliance. Aging alters the composition of the venous wall (2), and there is indirect evidence that calf venous compliance may be lower in older subjects (19, 23). In contrast, at least in young adults, calf venous compliance has been reported to be greater in endurance-trained humans compared with their sedentary peers (8, 20, 24). Taken together, these experimental observations suggest that habitual endurance exercise may attenuate the age-associated reductions in leg venous compliance in healthy adult humans.

In the present study, we used a noninvasive method of determining limb venous compliance (26) recently validated by Halliwill and colleagues (18) to test this hypothesis. This method overcomes important limitations in previous approaches to measuring leg venous compliance in humans (18). Calf venous compliance was determined in healthy young and older men who either were sedentary or regularly performed endurance (primarily leg) exercise.

METHODS

Subjects. Thirty-two healthy men were studied. Subjects were classified as either “young” (20–35 yr old) or “older” (55–75 yr old). On the basis of their exercise habits over the prior two years, subjects were further classified as “sedentary” (no regular physical activity) or “endurance exercise trained” (strenuous endurance exercise ≥5 days/wk). The latter subjects all performed leg exercise, primarily running. Of the young endurance-trained subjects seven of eight were runners and all of the older endurance-trained subjects were runners.

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Subjects were healthy based on medical history, had a resting arterial blood pressure <140/90 mmHg, did not smoke, were not obese (body mass index <30 kg/m²), were not taking any medications known to affect cardiovascular function, and had no history or symptoms of venous deficiency. Older subjects were further evaluated for overt cardiovascular disease via physical examination and resting and maximal treadmill exercise electrocardiograms (ECG).

The experimental protocol was approved by the Human Research Committee of the University of Colorado at Boulder. Written informed consent was obtained from participants after the nature, purpose, and risks were explained.

Measurements. Subjects refrained from caffeine ingestion for 12 h and food consumption for 4 h before testing. Endurance-exercise-trained subjects were studied the day after their last exercise bout to control for possible acute effects of aerobic exercise on calf venous compliance.

Maximal oxygen consumption. Maximal aerobic capacity was determined during incremental treadmill exercise to exhaustion using open-circuit spirometry as described previously (30).

Resting arterial blood pressure and heart rate. Resting arterial blood pressure was measured noninvasively over the brachial artery (Dinamap XL, Johnson & Johnson; Arlington, TX) in the supine position. The average of three consecutive measures is reported. Heart rate at rest was determined during the same period from the ECG.

Body composition. Body fat percentage was determined using dual-energy X-ray absorptiometry (Lunar Radiation; Madison, WI).

Calf volume. Calf volume was calculated from four anthropometric girth measures equidistantly obtained from the calf, from the medial malleolus to the tibial plateau, and one calf segment length over this same region. The four girth measures were averaged together, and the mean radius was determined. This radius (r) in addition to the calf segment length (L) were then used to algebraically calculate calf volume (πr²L). This technique produces results highly correlated (R = 0.94) with direct volumetric displacement (K. D. Monahan, unpublished data).

Venous compliance plethysmography. Changes in calf volume were measured noninvasively using strain-gauge plethysmography (EC4, D. E. Hokanson; Bellevue, WA) at the maximal calf circumference. Mercury-in-Silastic strain gauges were calibrated to determine changes in limb volume relative to baseline. A venous collecting cuff (D. E. Hokanson) was placed ~5 cm proximal to the knee. Venous collecting cuff pressure was measured directly with a Stratham pressure transducer (Ohmeda; Louisville, CO) positioned in line with the venous collecting cuff and air source.

Protocol. Subjects rested supine for 30 min before data acquisition. Subjects were instrumented for simultaneous measurement of calf volume change (strain-gauge plethysmography) and venous collecting cuff pressure. Each subject’s right leg was positioned above heart level to promote venous drainage and was supported at the ankle and thigh. Calf venous compliance was measured via the method of Robinson and Wilson (26) as modified by Halliwill et al. (18). After instrumentation and rest, venous collecting cuff pressure was applied at 60 mmHg for 8 min and then reduced at a rate of 1 mmHg/s (over 1 min) to 0 mmHg (Fig. 1).

Data analysis. Data for assessment of calf venous compliance were collected after analog-to-digital conversion at 50 Hz (CODAS, Dataq Instruments; Akron, OH) onto a PC computer for later analysis. Determination of venous compliance was performed as described previously (18). Specifically, pressure-volume curves were generated from the pressure-volume relation as pressure was decreased at a rate of 1 mmHg/s from 60 mmHg to 10. Data below 10 mmHg were excluded due to the ambiguity of true venous pressure at low cuff pressures. Pressure-volume curves were compared by means of the quadratic regression model (Δlimb volume) = βo + β1·(cuff pressure) + β2·(cuff pressure)². For the model, Δlimb volume was equal to limb volume at a given cuff pressure minus baseline limb volume (i.e., before cuff inflation). Regression models were calculated using the SAS GLM procedure (SAS v6.09, SAS Institute; Cary, NC), including intrasubject repeated measures for cuff pressure and Δlimb volume and intersubject classifications for age and training status. For each subject, data from 60 to 10 in 2-mmHg increments were included in the regression. Because the pressure-volume relation is not linear, a single number is not sufficient to characterize the slope of the pressure-volume curve. Thus the group-average regression parameters β1 and β2 were used together as an estimate of compliance, such that compliance = β1 + 2·β2·(cuff pressure). That is, compliance was defined as the derivative of the pressure-volume curve. The resulting pressure-dependent “compliance lines” were evaluated graphically.

To further explore the relation between venous compliance and subject characteristics, univariate correlations were determined using values for calf venous compliance at an arbitrary pressure of 20 mmHg (i.e., Compliance20 mmHg = β1 + 2·β2·20). All data are presented as means ± SE.

RESULTS

Subject characteristics. Physical characteristics of subjects are presented in Table 1. There were no group differences in systolic blood pressure or calf volume. Body mass was unrelated to age, but was lower in endurance exercise-trained men (P < 0.05). Body fat percentage was higher with age, but lower in the trained men (P < 0.05). Diastolic blood pressure was unrelated to exercise status but, although well within
the normotensive range, was slightly higher in the older men ($P$, 0.05). Maximal oxygen consumption was lower with age ($P$, 0.05), but higher in endurance exercise-trained men ($P$, 0.05). Heart rate at rest was unrelated to age, but was lower in the trained men ($P$, 0.05).

**Calf venous compliance.** In older men in both groups, pressure-volume curves derived from the calf were less steep than in young men ($P$, 0.01) indicating lower venous compliance (Fig. 2 and Table 2). With age, leg venous compliance was $\sim$40% lower in sedentary men and $\sim$20% lower in endurance exercise-trained men. At both ages in the endurance-trained men, pressure-volume curves in the calf were steeper than in sedentary men ($P$, 0.01), indicating greater ($\sim$70–120%) venous compliance in the exercise-trained men (Fig. 3 and Table 2; interaction: $P$, 0.08). Indeed, calf venous compliance was $\sim$30% greater in the older endurance-trained men than in young sedentary men ($P$, 0.01).

**Correlations.** Because venous compliance is pressure dependent, univariate correlations were determined using values for calf venous compliance at an arbitrary pressure of 20 mmHg ($\text{Compliance}_{20\text{ mmHg}} = \beta_1 + 2\cdot\beta_2\cdot P$). In all subjects pooled, calf venous compliance was positively related to maximal oxygen consumption ($r$, 0.70; $P$, 0.05) and inversely related to calf volume ($r$, $-0.45$; $P$, 0.05) (Fig. 4).

**DISCUSSION**

The primary new findings from the present study are as follows. First, calf venous compliance is reduced

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young</th>
<th>Older</th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>$27 \pm 1$</td>
<td>$65 \pm 1^*$</td>
<td>$27 \pm 1$</td>
<td>$63 \pm 2^*$</td>
</tr>
<tr>
<td>Height, cm</td>
<td>$176 \pm 3$</td>
<td>$173 \pm 2$</td>
<td>$177 \pm 2$</td>
<td>$169 \pm 3^*$</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>$76.1 \pm 3.0$</td>
<td>$79.1 \pm 3.2$</td>
<td>$74.8 \pm 2.0$</td>
<td>$71.1 \pm 2.2^*$</td>
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<tr>
<td>Body fat, %</td>
<td>$20 \pm 2$</td>
<td>$28 \pm 2^*$</td>
<td>$10 \pm 1^*$</td>
<td>$17 \pm 1^*$</td>
</tr>
<tr>
<td>VO$_2$ max, ml.kg$^{-1}$.min$^{-1}$</td>
<td>$45 \pm 2$</td>
<td>$29 \pm 2^*$</td>
<td>$62 \pm 2^*$</td>
<td>$45 \pm 1^*$</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>$115 \pm 2$</td>
<td>$120 \pm 3$</td>
<td>$115 \pm 2$</td>
<td>$117 \pm 3$</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>$65 \pm 2$</td>
<td>$74 \pm 2^*$</td>
<td>$63 \pm 2$</td>
<td>$71 \pm 1^*$</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>$61 \pm 2$</td>
<td>$61 \pm 3$</td>
<td>$47 \pm 2^*$</td>
<td>$47 \pm 1^*$</td>
</tr>
<tr>
<td>Calf volume, ml</td>
<td>$2,524 \pm 144$</td>
<td>$2,510 \pm 153$</td>
<td>$2,318 \pm 170$</td>
<td>$2,367 \pm 95$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE; $n$ = 8 subjects for all groups. VO$_2$ max, maximal oxygen consumption; BP, blood pressure. $^*$ $P$, 0.05 vs. young men of same physical activity status; $^\dagger$ $P$, 0.05 vs. age-matched sedentary men.

Fig. 2. Pressure-volume (top) and pressure-compliance relations (bottom) in young (left) and older men (right).
with age in both healthy sedentary and endurance exercise-trained men, suggesting that these changes are, at least in part, primary effects of human aging. Second, the magnitude of the age-associated decline in calf venous compliance appears to be only half as great in men who exercise regularly compared with their sedentary peers. Third, calf venous compliance is greater in both young and older endurance exercise-trained compared with age-matched sedentary men. Fourth, the finding that older endurance-trained men demonstrate elevated calf venous compliance compared with young sedentary men suggests that a sedentary lifestyle may have a greater negative influence on venous compliance than aging per se. Overall, our results provide experimental support for both independent and interactive effects of aging and habitual exercise status on leg venous compliance in adult humans.

The present findings are consistent with, but significantly extend, those of previous investigations concerning the effects of age or exercise training on leg venous compliance (8, 15, 20, 22, 33). First, our experimental approach to the measurement of calf venous compliance avoided some of the key limitations of previous methods (see Methodological considerations). As such, our data provide more direct and definitive evidence for the independent influences of age (negative) and endurance-exercise training (positive) on leg venous compliance in adult humans. Second, the present results are the first to our knowledge demonstrating: 1) a positive association between regular exercise and leg venous compliance in older adults, and 2) independent and interactive influences of age and habitual exercise status on leg venous compliance.

Methodological considerations. Methods for assessing limb venous compliance in vivo involve venous collection in a dependent limb via application of an externally applied pressure cuff proximal to the elbow or the knee. This collecting cuff pressure restricts venous outflow, minimally impedes arterial inflow, and causes venous distention, which is initially mediated by increases in venous volume. Thus the ratio of the

Table 2. Pressure-volume regression parameters

<table>
<thead>
<tr>
<th>Sedentary</th>
<th>ΔLimb Volume = β₀ + β₁(Cuff Pressure) + β₂(Cuff Pressure)²</th>
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<tbody>
<tr>
<td>Young</td>
<td>ΔLimb volume = 0.973 ± 0.269 + 0.094 ± 0.017(Cuff pressure) − 0.00082 ± 0.00024(Cuff pressure)²</td>
</tr>
<tr>
<td>Older</td>
<td>ΔLimb volume = 0.918 ± 0.167 + 0.057 ± 0.011(Cuff pressure) − 0.00042 ± 0.00015(Cuff pressure)²</td>
</tr>
<tr>
<td>Trained</td>
<td>ΔLimb volume = 1.276 ± 0.458 + 0.159 ± 0.029(Cuff pressure) − 0.00148 ± 0.00041(Cuff pressure)²</td>
</tr>
<tr>
<td>Young</td>
<td>ΔLimb volume = 0.998 ± 0.285 + 0.129 ± 0.018(Cuff pressure) − 0.00112 ± 0.00025(Cuff pressure)²</td>
</tr>
<tr>
<td>Older</td>
<td>ΔLimb volume = 1.018 ± 0.167 + 0.159 ± 0.029(Cuff pressure) − 0.00148 ± 0.00041(Cuff pressure)²</td>
</tr>
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See text for parameter details. *P < 0.05 vs. young men of same physical activity status; †P < 0.05 vs. age-matched sedentary men.
change in volume to the change in pressure (ΔV/ΔP) has been used to estimate venous compliance in a limb. The validity of such techniques is based on at least three major assumptions: 1) resting venous pressure is equal to zero; 2) volume change in a limb segment is due to increases in venous volume per se and not transcapillary filtration of plasma volume; and 3) externally applied venous collecting cuff pressure is equal to venous pressure at the time of measurement. It is highly likely, however, that one or more of these critical assumptions are violated using these approaches. For example, resting venous pressure is not equal to 0 mmHg in humans (18); thus the assumption that ΔP is equal to externally applied cuff pressure is problematic, because the true ΔP is assumed and not measured. Moreover, these techniques further assume that the volume changes measured represent alterations in venous volume. However, transcapillary filtration occurs in veins when venous transmural wall pressure is increased. The resulting transcapillary filtration produces a significant change in volume of the limb segment, but it is not a change in venous volume per se (27). Finally, the critical assumption that the externally applied venous collecting cuff pressure is equal to venous pressure at the time of measurement must be met. However, recent findings from one of the authors demonstrated how misleading plethysmographic recordings can be in determining when venous pressure is equal to venous collecting cuff pressure (18).

The method used in the present investigation does not depend critically on these assumptions. Calf venous compliance is only reported over the pressure range of 10–60 mmHg, thus avoiding ambiguous results obtained when lower pressures are used because venous pressure is unknown. Transcapillary filtration should occur based on the level of venous collecting pressure and period of venous collection. However, because of the rapid period of measurement (~60 s), the ability for filtrate to reenter the vasculature is small and thus the volume changes observed result primarily from alterations in venous volume. Finally, under the experimental conditions of the present study the assumption that venous collecting cuff pressure is equal to venous pressure appears valid (18).

Potential mechanisms. We can only speculate on the mechanism(s) responsible for the age-related reductions in calf venous compliance in sedentary and endurance-trained men. A strong prevailing view is that the muscle mass surrounding the deep calf veins plays a primary role, such that greater muscle mass is associated with lower calf venous compliance and vice versa (7). Consistent with this, in the present study, we found a significant inverse relation between calf venous compliance and calf volume in the pooled group (r = −0.45). This association persisted in subgroup analyses of young sedentary (r = −0.73) and young endurance-trained (r = −0.56, all P < 0.05) men, but not in either group of older men (P > 0.05). However, we feel that differences in calf muscle mass cannot explain our observations. First, calf venous compliance is lower with age in both sedentary and endurance-trained men, whereas calf volume is unchanged with age. Second, although not measured in the present study, calf muscle mass is most likely either unchanged or reduced with age in sedentary and endurance-trained humans, similar to the reductions observed in total body and whole leg, fat-free mass in these two populations (14). This should result in increased rather than decreased calf venous compliance with age. Instead, we postulate that alterations in the composition of the venous wall represent the most likely cause of age-related reductions in calf venous compliance in healthy humans. In this context, a decrease in the ratio of elastin to collagen in the venous wall has been observed with age that would act to reduce compliance (2).

The mechanism(s) involved in the ability of endurance-exercise training to enhance calf venous compliance has not been determined. Similarly, augmented vascular compliance has been observed recently in the arterial circulation with endurance exercise training (31). Regular exercise may increase tonic nitric oxide bioavailability from the vascular endothelium (30a) and/or reduce sympathetic α-adrenergic vasomotor tone (4). Whether venous smooth muscle tone is affected by regular endurance exercise via one or more of these mechanisms is currently unknown. However, it has recently been demonstrated that sympathetic ac-
tivation (and presumably increases in smooth muscle cell tone) reduces unstressed venous volume, but does not affect venous compliance (18). Thus we speculate that alterations in the composition of the venous wall (e.g., changes in collagen cross-linking, elastin-to-collagen ratio, etc.), rather than differences in venous smooth muscle tone, may explain the apparent modulatory influence of endurance exercise training on calf venous compliance.

Significance. The findings of the present study may have important physiological and clinical significance. Elevated calf venous compliance in endurance-trained men was observed in both young and older subjects. This elevation in calf venous compliance may partially explain the greater incidence of orthostatic intolerance reported in endurance-trained adults (25). In the context of the present findings, it is interesting to note that endurance-trained humans demonstrate augmented cardiovagal baroreflex sensitivity (9, 10, 21) and blood volume (6), which should assist in the regulation of arterial blood pressure during orthostatic stress. Furthermore, the observation that calf venous compliance is reduced with age in sedentary men may explain the paradoxical observation that these individuals tolerate orthostatic stress as well as their younger counterparts (29, 32), despite reduced levels of cardiovagal baroreflex sensitivity (16, 21), blood volume (11), and reduced limb vasoconstriction in response to increases in muscle sympathetic nerve activity (12). Taken together, this may emphasize the importance of calf venous compliance in determining orthostatic tolerance. It appears plausible to speculate that elevated calf venous compliance would be associated with a greater hemodynamic stress (reductions in central blood volume) and a greater compromise in cardiac preload, predisposing these individuals to blood pressure dysregulation and syncopal episodes. Consistent with this speculation, it appears that central blood volume shifts (estimated with thoracic impedance) are attenuated with age in humans during application of lower body negative pressure (29).

Finally, our findings also may have important implications for studies using orthostatic stress to assess autonomic function in groups that may differ in venous compliance. Specifically, application of similar orthostatic stress may not produce similar levels of hemodynamic stress (i.e., reductions in central blood volume and mean arterial pressure) if differences in calf venous compliance are present, as recently demonstrated in young and older adults (23). Furthermore, cardiovascular responses to orthostatic stress can be nearly abolished by reducing/limiting the translocation of fluid into the legs of humans (17). These observations emphasize the importance of calf venous compliance in determining the level of hemodynamic stress applied during orthostasis and have been largely ignored in the past.

Limitations. The reader should be aware of several limitations associated with the present study. First, the venous collecting cuff pressure was used as a surrogate for venous pressure in the present study. Measures of venous compliance depend critically on the confidence that this assumption is met. Halliwill and colleagues (18) demonstrated that venous pressure reaches levels of venous collecting cuff pressure within 4 min. Because we studied subjects varying in age and thus whole leg blood flow (13), the rate of filling of calf veins may have varied among our groups based on the association between arterial inflow and venous volume changes (18). Accordingly, the venous collection period was extended to twice that suggested for young subjects to control for this potential confound. Thus we feel the assumption that venous pressure was equal to venous collecting cuff pressure was met because collection period was doubled (from 4 to 8 min) to account for a presumed ~30% difference in femoral (leg) blood flow. Additionally, it has been demonstrated that increased transcapillary filtration with an extended period of venous collection does not alter limb compliance (18). Second, we studied only leg exercise-trained subjects. It is possible, perhaps even likely, that any adaptation to endurance exercise is mediated locally (in the trained limbs). If so, augmented leg venous compliance may not be observed in upper body exercise-trained individuals. Finally, we studied only healthy men. Therefore, our results cannot be generalized to women or patients with chronic cardiovascular or other disease states.

In conclusion, to the best of our knowledge these data are the first to provide direct experimental support for the hypotheses that leg venous compliance 1) is reduced with age in both sedentary and endurance exercise-trained men; 2) is better preserved with age in the regularly exercising men; 3) is greater in young and older endurance exercise-trained compared with age-matched sedentary men; and 4) that older endurance-trained men demonstrate elevated levels of venous compliance compared with young sedentary men. These findings related to age- and habitual exercise-modulation of leg venous compliance may have important implications regarding arterial blood pressure regulation during orthostatic stress as well as during exercise in healthy adult humans.

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REFERENCES


