Limb venous tone and responsiveness in hypertensive humans

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1Department of Health, Nutrition, and Exercise Sciences, University of Delaware, Newark, Delaware; 2Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, Missouri; and 3Christiana Care Health Services, Cardiovascular Clinical Trials, Newark, Delaware

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Delaney EP, Young CN, DiSabatino A, Stillabower ME, Farquhar WB. Limb venous tone and responsiveness in hypertensive humans. J Appl Physiol 105: 894–901, 2008. First published July 17, 2008; doi:10.1152/japplphysiol.90574.2008.—Hypertensive (HTN) animal models demonstrate lower venous compliance as well as increased venous tone and responsiveness compared with normotensive (NTN) controls. However, the extent to which findings in experimental animals can be extended to humans is unknown. Forearm and calf venous compliance were quantified in 9 NTN (23 ± 1 yr) and 9 HTN (24 ± 1 yr) men at baseline, after administration of nitroglycerin (NTG), during a cold pressor test (CP), and post-handgrip exercise ischemia (PEI). Individual pressure-volume relationships from a cuff deflation protocol (1 mmHg/s) were modeled with a quadratic regression. Regression parameters β1 and β2 were used to calculate compliance. A one-way ANOVA was used to compare the beta parameters and a repeated-measures ANOVA was used to compare volumes across all pressures (between groups at baseline and within groups during perturbations). Limb venous compliance was similar between groups (forearm: NTN β1 = 0.11 ± 0.01 and β2 = −0.00097 ± 0.0001; HTN β1 = 0.10 ± 0.01 and β2 = −0.00088 ± 0.0001); calf: NTN β1 = 0.12 ± 0.01 and β2 = −0.00102 ± 0.0001; HTN β1 = 0.11 ± 0.01 and β2 = −0.00090 ± 0.0001). However, at baseline, volume across all pressures (i.e., capacitance) was lower in the forearm (P ≤ 0.01) and tended to be lower in the calf (P = 0.08) in HTN subjects. Venous compliance was not altered by any perturbation in either group. Forearm volume was increased during NTG in HTN subjects only. While venous compliance was similar between NTN and HTN adults, HTN adults have lower forearm venous capacitance (volume) which is increased with NTG. These data suggest that young HTN adults may have augmented venous smooth muscle tone compared with NTN controls.

Reduced venous compliance has been found (9, 24, 33, 35) in HTN animals. In addition, there is evidence that venous distensibility and capacitance are reduced in HTN animals (24, 33, 35, 42). Indeed, several animal models of hypertension, including DOCA-salt (40), Goldblatt hypertension (42), spontaneously HTN rats (20) and chronic low-dose ANG II HTN rats (17), demonstrate increased venomotor tone. This augmentation in venomotor tone in HTN animals could be the result of increased sympathetic vasoconstriction, as the differences are abolished with ganglionic blockade (9). In addition, HTN animals demonstrate increased venous reactivity to norepinephrine compared with normotensive (NTN) controls (40). Bevan et al. (5) observed enhanced venous responsiveness and sensitivity to norepinephrine using an in vitro model of HTN rabbit veins. These findings suggest that veins may have an exaggerated response to sympathetic activation that may underlie augmented venous tone in hypertension. In addition, a study by Trippodo (37) found that total circulatory compliance was reduced in rats with an infusion of epinephrine, indicating that sympathetic activation can reduce compliance. However, the extent to which findings in experimental animals can be extrapolated to HTN humans remains unknown.

In humans, arterial compliance is reduced in hypertension (18, 21, 30). With regard to the venous side of the circulation, studies in HTN humans have reported discrepant results with some finding decreased peripheral venous compliance (19, 36) and others reporting no reduction in venous compliance in HTN adults (14, 39). In addition, the influence of the sympathetic nervous system on venous compliance in HTN humans has not been examined. This is an important question, considering that HTN humans have increased muscle sympathetic nerve activity (2, 32, 41) as well as elevated norepinephrine (32, 41), indicating an overactive sympathetic nervous system. Previous studies in NTN humans indicate that limb venous compliance is not acutely altered in response to perturbations designed to elicit non-baroreflex-mediated sympathoexcitation (cold pressor stimulus or post-handgrip exercise ischemia) (10, 12, 22, 43, 44). However, based on the finding of an overactive sympathetic nervous system in HTN humans and augmented venous reactivity in HTN animals, it is possible that sympathoexcitation may alter venous reactivity in HTN humans.

Given this background, the purpose of this study was to investigate the effects of hypertension on venous compliance in young adults. We hypothesized that venous compliance would be reduced in HTN compared with NTN subjects at baseline. An additional purpose of this study was to examine venous

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smooth muscle tone and responsiveness in HTN humans. To examine venous smooth muscle tone, we evaluated venous compliance after the administration of sublingual nitroglycerin (NTG); our hypothesis was that venous compliance would be acutely increased in HTN patients in response to this perturbation. To examine venous smooth muscle responsiveness, we also examined venous compliance during two distinct sympathetic stimuli [cold pressor (CP) test and post-handgrip exercise ischemia (PEI)]; we hypothesized that venous compliance would be acutely reduced in HTN patients during sympathoexcitation.

METHODS

Subjects

Nine HTN and 9 NTN men between the age of 18 and 30 yr of age were recruited for this study. HTN was defined as use of antihypertensive medications or untreated systolic blood pressure (SBP) above 140 mmHg or diastolic blood pressure (DBP) above 90 mmHg or at least three separate occasions (8). Six of the HTN subjects were untreated. The medications of the remaining three subjects were beta-blocker (n = 1), calcium channel blocker (n = 1), alpha-blocker (n = 1), and angiotensin receptor blocker (n = 1). All subjects gave written consent before participation. This study was approved by the Human Subjects Review Board of the University of Delaware.

Screening Session

A fasting blood sample was taken to measure liver enzymes (alanine aminotransferase and aspartate aminotransferase), kidney function (creatinine and blood urea nitrogen), a lipid profile, fasting glucose, and a complete blood count. Height and weight were measured and used to calculate body mass index (BMI). Resting blood pressure and 12-lead ECG were obtained. To ensure that the subjects were healthy and used to calculate estimated peak oxygen consumption (V̇O₂peak) (3). Total exercise time and heart rate were used to calculate body mass index (BMI). Resting blood pressure and 12-lead ECG were obtained. To ensure that the subjects did not have overt coronary artery disease, they completed a submaximal Bruce protocol treadmill test to 85% maximal heart rate ([220 – age] * 0.85) (3). Total exercise time and heart rate were used to estimate time to age-predicted maximal heart rate, and this value was used to calculate estimated peak oxygen consumption (V̇O₂peak) (3).

Exclusion criteria included forms of cardiovascular disease, other than HTN; pulmonary, liver, metabolic, or kidney disease; neurological disease; cancer; tobacco use; abnormal ECG during exercise or at rest; and obesity (BMI ≥ 30 kg/m²).

Experimental Visit

Subjects refrained from taking all antihypertensive medication 2 days before the experimental visit in conjunction with a collaborating cardiologist and their primary care physician. Subjects were instructed to avoid food, caffeine, exercise, and alcohol for at least 12 h before arriving at the laboratory. On arrival, subjects were equipped with a single-lead ECG (Dinamap Dash 2000, GE Medical Systems, Milwaukee, WI). Beat-by-beat blood pressure was measured by placing a cuff on the middle finger of the nondominant hand, which was calibrated to an upper arm cuff according to the manufacturer’s return-to-flow calibration instructions (Finometer, Finapres Medical Systems, The Netherlands). The Finometer has been shown to track acute changes in arterial blood pressure and is strongly correlated to intra-arterial radial pressure (26). In a subgroup of subjects, a 20-gauge, 5-cm intravenous catheter was placed into the antecubital area of the dominant forearm and connected to a pressure transducer (DT-12, Becton Dickinson, Temse, Belgium) for the direct measurement of venous pressure.

Mercury-in-Silastic strain gauges were placed around the dominant forearm and corresponding calf at the point of maximal girth and connected to a plethysmograph (model EC6, Hokanson, Bellevue, WA) for the assessment of changes in limb volume. Congestion cuffs were placed around the upper arm and thigh and connected to a rapid cuff inflator (model E-20, Hokanson) that was attached to an external air source (model AG101, Hokanson). To promote venous drainage, the limbs were placed slightly above heart level.

Protocol

Subjects were in a supine position for at least 30 min before 2 min of resting heart rate and blood pressure data were collected. Venous compliance was measured according to the methods of Hall will et al. (12). Limb cuffs were rapidly inflated and maintained at 60 mmHg for 8 min. At the end of the 8-min inflation period, the cuffs were deflated at 1 mmHg/s for 60 s to 0 mmHg. Baseline measurements were made first, and the remaining three trials were performed in random order with 15 min of quiet rest between each trial.

Baseline. Venous compliance was assessed under resting conditions.

Sublingual NTG administration. Four minutes into the inflation period, 0.3 mg of NTG was administered sublingually. Four minutes later the 60-s deflation period began, coinciding with the time of peak nitric oxide concentration (13).

CP stimulus. Seven minutes into the inflation period, the foot of the noninstrumented leg was immersed and remained in ice water for the last minute of the inflation period and during the deflation period (2 min total).

PEI. Venous compliance was measured in the leg only during this trial. Four minutes into cuff inflation, subjects performed rhythmic handgrip exercise with the dominant hand at 60% maximal contraction, 40 contractions/min (using a metronome), for a duration of 3 min. At the end of the 3-min period, an occlusion cuff on the upper arm was inflated to suprasystolic blood pressure (>200 mmHg) to induce ischemia for the last minute of the inflation period and during the 60-s deflation of the limb cuff.

Data Analysis

Volume measured during cuff deflation was binned into 2-mmHg increments from 60 to 10 mmHg using custom MatLab software (MatLab 6.5). These data were then graphed against pressure and analyzed on an individual basis using the following quadratic regression equation (Sigma Plot 9.0):

\[ \Delta \text{Limb Volume} = \beta_0 + \beta_1 \cdot (\text{cuff pressure}) + \beta_2 \cdot (\text{cuff pressure})^2 \]

\( \beta_0 \) is often used as an index of venous capacitance. Venous capacitance can be defined as the relationship between total contained volume and the transmural distending pressure of the vasculature (29); with this definition, it is difficult to describe capacitance using a single number (25). Therefore, we used limb volume across the pressures from 60 to 10 mmHg as an index of venous capacitance. In this protocol, cuff pressure was used as an index of transmural distending pressure.

Venous compliance was then calculated using the quadratic parameters \( \beta_1 \) and \( \beta_2 \) for pressures between 60 and 10 mmHg using the following equation:

\[ \text{Compliance} = \beta_1 + \beta_2 \cdot (\text{cuff pressure}) \]

Compliance can be defined as the ratio of change in contained volume to the ratio of change in transmural distending pressure (29). Therefore, capacitance is represented by the whole pressure-volume curve (volume across all pressures), while the slope of this curve represents compliance. Compliance was also graphed against pressures and presented along with the pressure-volume curves.

Statistics

An unpaired t-test was used to detect group differences in subject characteristics and an ANOVA was used to detect differences in regression parameters between groups as well as changes in regression parameters within groups as a result of the perturbations. A
repeated-measures ANOVA was used to detect group differences in forearm and calf volume across pressures from 60 to 10 mmHg at baseline as well as the effect of the perturbations on forearm and calf volume within each subject group. All data are reported as means ± SE, and a P value of ≤0.05 was considered statistically significant for all variables.

RESULTS

Subject characteristics are located in Table 1. SBP and DBP in Table 1 represent the blood pressure of all HTN subjects after the medication-free period. By design, the HTN subjects had higher mean arterial pressure (MAP), SBP, and DBP than NTN subjects. All HTN subjects had an SBP > 140 mmHg while only two had both SBP > 140 mmHg and DBP > 90 mmHg. These pressures indicate that the 2-day withdrawal of antihypertensive therapies was sufficient to increase BP to HTN levels. The average BP of the treated HTN subjects while on medication was 132/74 mmHg. There was no difference in age, height, weight, BMI, or estimated VO²peak between HTN subjects; however, this did not reach statistical significance (P = 0.08 and P = 0.10, respectively).

Table 2. Forearm pressure-volume regression parameters β₀, β₁, and β₂

<table>
<thead>
<tr>
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<th>β₀</th>
<th>β₁</th>
<th>β₂</th>
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<tr>
<td><strong>Normotensive</strong></td>
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<td>Baseline</td>
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<td><strong>Hypertensive</strong></td>
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<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>0.74±0.27*</td>
<td>0.101±0.009</td>
<td>−0.00088±0.00009</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>1.59±0.24†</td>
<td>0.100±0.006</td>
<td>−0.00089±0.00007</td>
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<tr>
<td>Cold pressor</td>
<td>0.56±0.37</td>
<td>0.092±0.006</td>
<td>−0.00076±0.00007</td>
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Values are means ± SE. *Significantly different from normotensive subjects, P < 0.05. †Significantly different from baseline, P < 0.05.

Table 3. Calf pressure-volume regression parameters β₀, β₁, and β₂

<table>
<thead>
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<th></th>
<th>β₀</th>
<th>β₁</th>
<th>β₂</th>
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<td>Postexercise ischemia</td>
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<td>0.118±0.012</td>
<td>−0.00099±0.00011</td>
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<tr>
<td><strong>Hypertensive</strong></td>
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</tr>
<tr>
<td>Baseline</td>
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<td>Nitroglycerin</td>
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<td>Cold pressor</td>
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<td>0.091±0.008</td>
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<td>Postexercise ischemia</td>
<td>1.29±0.34</td>
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<td>−0.00083±0.00009</td>
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Values are means ± SE. *Significantly different from baseline, P < 0.05.

Intravenous Pressure

Intravenous pressure was obtained in four NTN and seven HTN subjects. Resting venous pressure was 9.2 ± 2 mmHg in NTN subjects and 9.4 ± 1 mmHg in HTN subjects. Resting venous pressure was not different between NTN and HTN subjects. The slope of the relationship between congestion cuff pressure and intravenous pressure was 0.93 ± 0.02 in NTN subjects and 0.94 ± 0.03 in HTN subjects during baseline cuff deflation. The correlation coefficient was 0.999 ± 0.000 in NTN subjects and 0.998 ± 0.001 in HTN subjects. The slope and correlation coefficient were not different between NTN and HTN subjects. On the basis of these data, we determined that congestion cuff pressure could be used as a surrogate for intravenous pressure.

Baseline Venous Compliance

The quadratic parameters β₀, β₁, and β₂ for the forearm and calf are presented in Tables 2 and 3, respectively. Baseline forearm and calf venous compliance was similar between NTN and HTN subjects, as indicated by β₁ and β₂. The baseline pressure-volume and pressure-compliance graphs for the forearm are located in Fig. 1. Repeated-measures ANOVA indicated that volume across all pressures and β₀ were significantly lower in the forearm in HTN subjects (P < 0.05), indicating a reduced venous capacitance. Volume and β₀ tended to be lower in the calf of HTN subjects compared with NTN subjects; however, this did not reach statistical significance (P = 0.08 and P = 0.10, respectively).

NTG

Across all subjects, MAP and SBP were significantly lower than baseline during the NTG trial (NTN: MAP Δ = −2.6 ± 2 mmHg, SBP Δ = −5.8 ± 1 mmHg; HTN: MAP Δ = −3.6 ± 3 mmHg, SBP Δ = −9.3 ± 3 mmHg; P < 0.05). There was no change in DBP during the NTG trial (NTN: Δ = −0.8 ± 1 mmHg; HTN: Δ = −1.8 ± 2 mmHg; P > 0.05). Heart rate was increased from baseline during the NTG trial (NTN: Δ = 10 ± 3 beats/min; HTN: Δ = 7 ± 3 beats/min; P < 0.05). The changes in blood pressure and heart rate were not different between groups.

Forearm pressure-volume (top) and pressure-compliance (bottom) graphs at baseline and during the NTG trial are located in Fig. 2 for NTN (left) and HTN (right) subjects. There was no change in venous compliance in response to NTG administration in NTN or HTN subjects in the forearm (Fig. 2, bottom, and Table 2). However, forearm volume and β₀ increased significantly during the NTG trial in HTN (P < 0.05) but not NTN subjects. Calf volume and compliance were not different from baseline during the NTG trial in HTN or NTN subjects (Table 3).

Sympathoexcitation

Across all subjects, MAP, SBP, and DBP all significantly increased above baseline during the CP (NTN: MAP Δ =
DISCUSSION

This study investigated the effect of hypertension on venous compliance. We hypothesized that limb venous compliance would be reduced in HTN patients compared with well-matched NTN controls. Contrary to the initial hypothesis, venous compliance was similar between HTN and NTN groups; however, venous capacitance was reduced in the HTN subjects. In addition, we examined venous tone and responsiveness in HTN humans. Similar to NTN adults, venous compliance was not acutely altered by endothelium-independent venodilation or non-baroreflex-mediated sympathoexcitation in the HTN group. Interestingly, forearm volume was significantly increased in response to nitroglycerin in only the HTN adults, which may suggest chronically increased venous tone.

In animal models of hypertension, venous compliance is reduced compared with NTN controls (9, 24, 35), although this is not a universal finding (6). Similarly, in humans, some studies have found reduced peripheral venous compliance in hypertension (19, 36), while others have not (7, 14, 39). It is possible that differences in the methodologies used in these studies led to the discrepant results (i.e., inflation vs. deflation protocols). Furthermore, it is possible that differences in the duration of HTN contributed to these disparate findings. It is important to note that our subjects were young, otherwise healthy adults. Thus it is possible that reductions in peripheral venous compliance are apparent with longer standing hypertension than that of these subjects. Regardless of the finding of similar venous compliance between subject groups, we found that venous capacitance was reduced in HTN subjects.

Limb volume across all pressures during the cuff deflation protocol was reduced in the forearm and tended to be lower in the calf of HTN subjects (P = 0.08). This reduction in volume suggests a reduction in venous capacitance in hypertension. These results are consistent with a study conducted by Walsh et al. (38). However, it is unclear whether the reduction in venous capacitance in Walsh’s study was due to hypertension or whether it was related to the greater age of the HTN subjects. In the present study, we used only young NTN and HTN subjects (mean age 23 ± 1 and 24 ± 1 yr, respectively); therefore, age did not contribute the lower venous capacitance in HTN subjects. In addition, Simon et al. (34) and Takeshita and Mark (36) found pressure-volume curves of the forearm during venous occlusion plethysmography were shifted toward the pressure axis in HTN subjects. Moreover, systemic phen tolamine, an α-adrenergic antagonist, shifted the venous pressure-volume curve upward in HTN patients, while the pressure-volume curve remained unchanged in NTN subjects (36).

Thus similar to animal models of hypertension (9), it is possible that augmented venous tone contributes to the reduction in limb venous volume in HTN subjects.

Further support for chronically increased venous tone in the HTN subjects is evident when examining the results obtained during sublingual nitroglycerin administration. Nitroglycerin works through an endothelium-independent mechanism to elicit reductions in vascular smooth muscle tone, causing venodilation (1). As noted in Fig. 2, the pressure-volume relationship was shifted upward in the forearm after nitroglycerin administration in HTN subjects only. This upward shift indicates an increase in unstressed volume contained within the

![Baseline forearm pressure-volume (top) and pressure-compliance (bottom) curves in normotensive (NTN; ○) and hypertensive (HTN; ●) subjects. Forearm volume was significantly lower across all pressures in HTN subjects compared with NTN subjects (*P < 0.05). Values are means ± SE.](image-url)
forearm veins after nitroglycerin administration. Therefore, nitroglycerin essentially “normalized” the forearm capacitance in HTN subjects. In this study and previous studies from our lab, utilizing the same 0.3-mg dose as well as a higher dosage of 0.4 mg of nitroglycerin, we found no change in both calf and forearm volume in NTN subjects (43, 44). Thus this increase in forearm volume elicited by smooth muscle cell relaxation in HTN subjects, in addition to the baseline differences in limb

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**Fig. 2.** Forearm pressure-volume (top) and pressure-compliance (bottom) curves in NTN (left) and HTN subjects (right) at baseline (circles) and after nitroglycerin administration (triangles). Forearm volume was significantly increased above baseline after nitroglycerin administration in HTN subjects (*P < 0.05). Values are means ± SE.

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**Fig. 3.** Forearm pressure-volume (top) and pressure-compliance (bottom) curves in NTN (left) and HTN subjects (right) at baseline (circles) and during the cold pressor test (squares). Values are mean ± SE.
volume between the HTN and NTN subjects, may indicate that HTN humans have chronically increased venous tone. Interestingly, this increase in venous capacitance in response to endothelium-independent venodilation was not observed in the calf. However, this is not surprising, as previous studies have also observed differences in venous hemodynamics between the forearm and the calf (10, 12, 27, 44). In addition, calf veins are subjected to high hydrostatic pressures during orthostasis, while forearm veins are not (25). Therefore, calf veins may have a limited ability to vasodilate (in response to dilatory stimuli), as this could result in an unfavorable reduction of blood return to the heart. Finally, the effects of nitroglycerin have been shown to be specific to particular vascular beds, which may have led to the disparate findings in the forearm and calf veins in HTN subjects (4, 11). For example, Gascho et al. (11) found that forearm volume increased while calf volume tended to decrease in response to nitroglycerin administration in supine subjects.

A study by Journo et al. (15) examined venous responsiveness to a cold pressor test in NTN and HTN subjects (15). Venous tone was increased in response to the cold pressor test in all subjects. While the increase in tone was almost twice a great in HTN subjects, this did not reach statistical significance. In this study, we used a deflation protocol to examine the venous responsiveness to sympathoexcitation and also found no difference in the change in venous compliance between groups during the cold pressor test. Other studies have reported no change in venous compliance in response to cold pressor stimulus and postexercise ischemia in NTN adults (10, 12, 22, 43, 44). The present data are consistent with these findings, which can now be extended to young HTN adults.

Some (10, 12, 44) but not all (22, 43) studies in NTN subjects have shown a decrease in venous volume during both the cold pressor test and post-exercise ischemia. The methods used to quantify acute changes in venous volume vary between studies. Previous studies have visually inspected the pressure-volume curve for the point where volume shifted from rapid filling to slow filling as a point index of capacitance (22) or used $\beta_0$ as an index of capacitance or volume (12, 43, 44). While we did see a reduction in $\beta_0$ in NTN subjects during post-handgrip exercise ischemia, this is a complex variable that is difficult to interpret (12). $\beta_0$ can be influenced by a number of factors, including resting venous pressure, fluid leak, fluid accumulation as a result of congestion cuff inflation (12), venous creep, and the compliance of the limb ($\beta_1$ and $\beta_2$). Due to the limitation of $\beta_0$, we used venous volume across all pressures as an index of capacitance and did not see a change in venous capacitance during acute sympathoexcitation in either subject group. The reason that capacitance was not affected in our HTN subject group during the cold pressor test or postexercise ischemia is unknown but may involve the sympathetic nervous system. Since sympathetic outflow is higher at rest in hypertension (32, 41), acute sympathoexcitation may not be able to further decrease venous capacitance. However, these findings are limited to a cold pressor stimulus and postexercise ischemia, and therefore other sympathoexcitatory stimuli warrant further investigation, both in NTN and HTN populations.

It is important to note that the perturbations utilized to increase or decrease venous tone were applied after the congestion cuffs had been inflated for many minutes. This approach was used because the main focus of this study was to examine the pressure-volume relationship and not the capacitance of the veins. This allowed us to examine the venous compliance during cuff deflation, at a time when sympathoexcitation would be elevated (2nd min of cold pressor test, 2nd min of postexercise ischemia) and when the concentration of nitroglycerin had peaked (4 min after administration). It is
possible that employing these perturbations after the cuffs were inflated affected the volume response of the limb. For example, if the veins were already full when the sympathoexcitation was applied, it may have not been possible to reduce the volume at that point. However, this is probably not the case since other studies that applied a perturbation designed to increase sympathetic outflow after cuff inflation found a reduction in limb volume during sympathoexcitation (10, 12, 44).

In conclusion, the results of the present study indicate that limb venous compliance is similar between young, otherwise healthy HTN adults and NTN control subjects. However, limb venous capacitance is reduced in HTN adults, possibly due to increased venous smooth muscle tone. This finding is supported by a lower limb volume in HTN patients compared with NTN subjects, along with an increase in forearm volume in response to venous smooth muscle relaxation via nitroglycerin administration. Finally, venous compliance is not altered during sublingual nitroglycerin administration or by non-baroreflex-mediated sympathoexcitation in NTN or HTN subjects.

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GRANTS

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