

Evidence for Pressure-Independent Sympathetic Modulation of Central Pulse Wave Velocity

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Background—Whether the sympathetic nervous system can directly alter central aortic stiffness remains controversial, mainly because of the difficulty in experimentally augmenting peripheral vasoconstrictor activity without changing blood pressure.

Methods and Results—To address this limitation, we utilized low-level cardiopulmonary baroreflex loading and unloading shown previously to alter sympathetic outflow without evoking parallel hemodynamic modulation. Blood pressure and carotid-femoral aortic pulse wave velocity (cf-PWV) were measured in 32 healthy participants (24 ± 2 years; women: $n=15$) before and during 12-minute applications of low-level lower body negative pressure; -7 mm Hg) and lower body positive pressure; $+7$ mm Hg), applied in a random order. Fibular nerve microneurography was used to collect muscle sympathetic nerve activity (MSNA) in a subset ($n=8$) to confirm peripheral sympathetic responses. During lower body negative pressure, heart rate, blood pressure, stroke volume, cardiac output, and total peripheral resistance were not statistically different (all $P>0.05$); MSNA burst frequency ($+15\%$; $P=0.007$), total MSNA ($+44\%$; $P=0.006$), and cf-PWV ($\Delta+0.3 \pm 0.2$ m/s; $P<0.001$) increased. In total, 28 (88%) of participants observed an increase in cf-PWV greater than the baseline typical error of measurement. During lower body positive pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance were not statistically different (all $P>0.05$), though blood pressure increased ($P<0.05$) and pulse pressure decreased ($P=0.01$); MSNA burst frequency (-4% ; $P=0.37$), total MSNA (-7% ; $P=0.89$), and cf-PWV ($\Delta 0.0 \pm 0.2$ m/s; $P=0.68$) were not statistically different.

Conclusions—These findings provide evidence that acute elevations in peripheral sympathetic activity can increase central aortic PWV in young participants independent of a change in distending or pulsatile blood pressure or heart rate. (*J Am Heart Assoc.* 2018;7:e007971. DOI: 10.1161/JAHA.117.007971.)

Key Words: arterial stiffness • autonomic nervous system • blood pressure • muscle sympathetic nerve activity

Elevated aortic stiffness is an independent predictor of cardiovascular events and all-cause mortality in healthy¹ and diseased^{2,3} populations. The mechanisms responsible for increased central artery stiffness, measured most commonly as carotid-femoral pulse wave velocity (cf-PWV),⁴ are not fully understood and complex. Arterial stiffening can involve the interplay of both mechanical (eg, blood pressure changes) and structural (eg, vessel wall composition) processes that acutely or chronically affect arterial viscoelasticity through changes in

the stress-strain relationship.^{5,6} An important consideration for experimentally probing potential mechanisms responsible for arterial stiffening is the known blood pressure dependency of central PWV measurements⁷; systolic blood pressure, mean arterial pressure, and pulse pressure are all strongly associated positively with central PWV.^{8–11}

One unresolved concept is whether activation of the sympathetic nervous system contributes to increases in arterial stiffness independent of changes in blood pressure. Observational data demonstrate that arterial stiffening coexists commonly with chronic elevations in basal sympathetic outflow in cardiovascular disease states.^{12–14} Similarly, arterial stiffening associated with healthy aging demonstrates similar relative increases in sympathetic outflow,^{15,16} though parallel changes in blood pressure occur also.^{8,9,11} Sympathetic outflow to the vasculature is known to elicit vasoconstriction at resistance vessels¹⁷ and is shown to alter the local vascular properties of large and medium conduit arteries.^{18–21} Importantly, the reductions in brachial artery distensibility with sympathetic activation occurred independent of changes in arterial pressure and diameter.²²

Correlational data suggest a pressure-independent relationship between peripheral sympathetic outflow and central PWV

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Clinical Perspective

What Is New?

- Prior prospective studies examining the effects of sympathetic activation on arterial stiffness have been confounded by experimental models that concomitantly alter blood pressure or heart rate.
- We utilized low-level lower body negative pressure to increase modestly muscle sympathetic nerve activity without changing blood pressure or heart rate, and observed parallel increases in central aortic pulse wave velocity.

What Are the Clinical Implications?

- These observations are relevant to understanding the acute and chronic factors that regulate central aortic stiffness, a prognostic marker of clinical risk.
- A pressure-independent role of peripheral sympathetic activation on arterial stiffness supports therapeutic targeting of central sympathetic outflow.

in young healthy subjects at rest.²³ However, experimental studies using classic sympathoexcitatory perturbations (eg, isometric handgrip, cold pressor test, lower body negative pressure [LBNP]) have reported both increases^{24–26} and no change^{27–29} in a variety of direct and indirect measures of arterial stiffness. Two recent studies using pharmacological autonomic ganglion blockade have reported no independent effect of inhibiting sympathetic outflow on central PWV.^{29,30} One commonality between all of these experimental approaches has been the inability to control experimentally for changes in arterial pressure (ie, modify peripheral sympathetic outflow without a change in blood pressure). This limitation has obscured the ability to determine the independent role of the sympathetic nervous system on arterial stiffness.

Therefore, the present study aimed to investigate whether pressure-independent changes in peripheral sympathetic outflow alter central and whole-body PWV. To address prior limitations, we utilized the application of low-level LBNP and lower body positive pressure (LBPP) shown previously to alter cardiac filling pressure and cardiopulmonary baroreflex control of peripheral sympathetic outflow directed towards skeletal muscle (muscle sympathetic nerve activity; MSNA)^{31,32} without changing stroke volume or arterial pressure.^{32–34} Based on these data, we hypothesize that (1) in response to non-hypotensive LBNP (−7 mm Hg), sympathetic activation will increase arterial stiffness; and (2) in response to non-hypertensive LBPP (+7 mm Hg), sympathetic outflow will decrease in parallel with arterial stiffness. These results will provide proof-of-principle for the capacity of peripheral vasoconstrictor outflow to modulate central arterial stiffness.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

Thirty-two healthy young (24 ± 2 years) participants were recruited for this study. Participants were all normotensive, nonsmoking, in sinus rhythm, free of known cardiovascular or metabolic disease, and not taking any long-term medications, with the exception of oral contraception ($n=4$). All procedures were approved by the University of Guelph Research Ethics Board and occurred following completion of informed written consent by each participant.

Experimental Protocol

Before the study visit, participants abstained from caffeine, alcohol, and strenuous exercise for 24 hours. Upon entering the temperature- and light-controlled laboratory following voiding, participants were positioned supine in a custom-designed lower body pressure tank sealed to the top of the iliac crest. The internal pressure of the lower body pressure tank was monitored using a calibrated commercial bidirectional pressure gauge (American Sensor Technologies Inc, Mt. Olive, NJ) and could be manipulated using a modified vacuum motor. After instrumentation and 5 minutes of quiet rest, participants completed a 10-minute baseline period. Subsequently, participants were randomized to the first designated pressure (LBNP or LBPP; ± 7 mm Hg), which was gradually applied over 30 s, and sustained for 12 minutes. Continuous measures of beat-to-beat blood pressure, heart rate, and whole body arterial stiffness (wb-PWV) were collected throughout the entire protocol. Six discrete brachial blood pressures were collected at 1-minute intervals at the onset of baseline and after minute 3 of the induced pressure stimulus. Immediately following discrete brachial blood pressure measurements, cf-PWV was measured at minute 7 and minute 9 during both baselines and at minute 9 and 11 during each pressure stimulus. In a subset of participants, continuous measures of MSNA were also collected over the entire duration of study to provide a direct marker of peripheral sympathetic activity.^{34,35} To permit all variables to return to baseline levels, participants were given at least 8 minutes of quiet rest before repeating the protocol with the alternate pressure stimulus.

Measurements

Three electrodes were placed on the torso to measure continuous heart rate using single-lead electrocardiography (ADInstruments Pty Ltd, Australia). Finger photoplethysmography (Finometer

MIDI, Finapres Inc, Netherlands) was used to measure beat-to-beat blood pressure by placing a cuff on the middle finger of the right hand. The Modelflow method enabled determination of beat-to-beat stroke volume³⁶ and subsequent calculation of cardiac output and total vascular resistance and conductance. To ensure consistency of absolute values, discrete brachial blood pressure was also collected using an automated oscillometric device (BPTru Medical Devices, Coquitlam, Canada) with a standard blood pressure cuff placed on the upper left arm.

Central arterial stiffness was assessed using the noninvasive criterion standard,⁴ cf-PWV. A commercial device (SphygmoCor; Model EM4C; AtCor Medical Pty Ltd, West Ryde, Australia) permitted simultaneous calculation of central pulse transit time through the use of a specialized pressure cuff placed around the proximal thigh and a pen-like applanation tonometer placed over the left carotid artery.³⁷ This methodology has been validated previously against the sequential tonometry method.³⁸ The distance between recording sites was obtained manually, as described.³⁸ Central pulse wave forms were collected over 20 cardiac cycles for determination of cf-PWV. If repeated cf-PWV recordings differed by >0.2 m/s, a third value was attained. The assessment of whole-body (wb)-PWV was determined using a high-fidelity piezoelectric transducer (Model TN1012/ST ADInstruments, Pty Ltd, Australia) placed on the first digit of the left foot, synchronized to the ECG to determine wb-pulse transit time. The distance between both landmarks was recorded from the sternal notch to the first digit of the plantar-flexed foot. The same 20 cardiac cycles were used for analysis of cf-PWV and wb-PWV. All continuous data were digitized and stored with LabChart (PowerLab, ADInstruments, Colorado Springs, CO) at a sampling frequency of 1000 Hz.

Muscle Sympathetic Nerve Activity

To confirm change in peripheral sympathetic outflow during low-level LBNP and LBPP, we collected microneurographic recordings of postganglionic MSNA in a subset of 11 participants. As described previously,^{34,35} a tungsten microelectrode (Frederick Haer, Brunswick, ME) was inserted percutaneously into the right peroneal nerve and adjusted until spontaneous pulse-synchronous multi-unit bursts of sympathetic activity were clearly observed from the background noise. A ground electrode was placed ≈ 2 cm away. The MSNA signal was amplified (75 000 \times), band-pass filtered (0.7–2.0 kHz), rectified, and integrated using a 0.1-s time constant to obtain the mean voltage multi-unit neurogram (Nerve Traffic Analyzer, Model 662C-4; Absolute Design and Manufacturing Services, Salon, IA). To confirm that the electrode site did not alter throughout the recording periods, the neural signal was monitored both audibly and visually. Custom semiautomated LabView software (National Instruments, Austin, TX) was used

to quantify MSNA burst frequency (bursts/min), and total MSNA (AU/min).^{34,35} Total MSNA was calculated as the product of mean burst area \times burst frequency; as each participant acted as their own control, we did not normalize the mean burst area data. Determination of a sympathetic burst was made based on a 3:1 signal-to-noise ratio and alignment with the time-shifted cardiac cycle.³⁹

Data and Statistical Analysis

Mean hemodynamic and MSNA data were calculated during the last 5 minutes of each baseline and during the last 3 minutes of each pressure stimulus. Mean arterial pressure was calculated as 1/3 systolic blood pressure plus 2/3 diastolic blood pressure. At baseline and each pressure stimulus, the 2 cf-PWV measurements were averaged. If a third measure was taken, the closest 2 cf-PWV measures were averaged. To permit the determination of wb-PWV, the time delay between pulse waves was determined by the difference between the R-wave of the ECG and the toe waveform from the piezoelectric sensor; the latter was band-pass filtered (5–30 Hz) for objective differentiation of the foot (ie, lowest point) of each waveform.⁴⁰

The primary study outcome was cf-PWV. An estimated effect size was calculated from prior work,²⁶ based on a Cohen's *d* of 0.5; it was estimated that 27 participants were required to achieve an assigned power of 80% and type I error rate of 5%. All analyses were performed using IBM SPSS Statistics 23 (Armonk, NY) and GraphPad Prism (GraphPad Software, La Jolla, CA). The Shapiro–Wilk test was used to determine the normality of all variables. Paired *t* tests were used to compare variables between baseline and each pressure stimulus (LBNP or LBPP); however, if violations of normality occurred, the Wilcoxon signed ranks test was used. For each variable, Cohen's *d* was calculated, representing small (0.2–0.5), moderate (0.5–0.8), and large (>0.8) effect sizes.⁴¹ Anticipating that low-level lower body pressure would evoke only modest changes in PWV, we determined the baseline typical error of measurement for both cf-PWV and wb-PWV, and classified participants as responders (ie, outside the typical error of measurement) and nonresponders (ie, inside the typical error of measurement). In addition, we calculated the reliability and variability of PWV measurements using the intraclass correlation coefficient and mean difference of repeated measurements of both cf-PWV and wb-PWV. The relationship between changes in cf-PWV and changes in MSNA burst frequency was tested with a Pearson correlation coefficient. Significance was defined as $P < 0.05$. All data are presented as mean \pm SD.

Results

The experimental protocol was completed and well tolerated by all participants. Fifteen participants were randomized to begin

with LBNP; 17 with LBPP. Eleven participants underwent microneurographic recordings; however, complete data were obtained only in 8 participants because of the inability to maintain a high-quality recording site during the pressure stimuli in 3 participants. Baseline age, body mass, height, and hemodynamic data were similar (all $P>0.05$) between these representative microneurography participants and the complete sample. In 2 participants, wb-PWV was not obtained because of technical issues. As expected, all hemodynamic, neural, and PWV measures were similar between both baseline periods (all $P>0.05$). Examination of within-baseline measures of cf- and wb-PWV displayed excellent reproducibility (intra-class correlation coefficient: 0.98 and 0.99, respectively) and small mean differences (0.04 ± 0.14 m/s and 0.02 ± 0.10 m/s, respectively). Reproducibility between baseline periods was similarly high (intraclass correlation coefficient: 0.94 and 0.91, respectively) with small mean differences (0.03 ± 0.22 m/s and 0.02 ± 0.29 m/s, respectively).

Lower Body Negative Pressure

All hemodynamic and neural variables demonstrated normal distributions. In confirmation of our model, heart rate, systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure, stroke volume, cardiac output, and total peripheral resistance (or conductance) were not statistically different during low-level LBNP (all $P>0.05$; Table 1). Modest sympathoexcitatory effects of LBNP (Table 1) were confirmed by increases in MSNA burst frequency (+15%; $P=0.007$; Cohen's $d=1.13$) and total MSNA (+44%; $P=0.004$; Cohen's $d=1.70$). During LBNP, central ($\Delta+0.3\pm 0.2$ m/s; $P<0.001$; Cohen's $d=1.35$) and whole body ($\Delta+0.2\pm 0.1$ m/s; $P<0.001$; Cohen's $d=1.25$) PWV were both elevated over baseline values (Figure 1). The increase in cf-PWV was greater than wb-PWV ($P=0.006$). The responses of both cf-PWV and wb-PWV during LBNP were not altered by any order effects (both $P>0.05$). Acknowledging the limited sample size and modest changes in each variable, correlational analysis was performed between the changes in cf-PWV and MSNA burst frequency ($r=0.58$, $P=0.14$).

To confirm that the changes in PWV during LBNP were not the result of random variations, we performed secondary analysis using the baseline typical error of measurement to group responders and nonresponders. The baseline typical errors of measurement for cf-PWV and wb-PWV were ± 0.09 m/s and ± 0.07 m/s, respectively. Using these values, 88% and 85% of the participant pool were defined as responders, having a cf-PWV or wb-PWV response greater than the typical error.

Lower Body Positive Pressure

All variables, with the exception of heart rate, cf-PWV, and total MSNA, demonstrated normal distributions. Heart rate,

Table 1. Hemodynamic and MSNA Measurements at Baseline and During Low-Level LBNP

	Baseline	LBNP	P Value	Cohen's d
Heart rate, bpm	56±8	56±8	0.19	0.22
Systolic blood pressure, mm Hg	105±8	105±8	0.84	-0.03
Diastolic blood pressure, mm Hg	65±6	66±6	0.10	0.28
Mean arterial pressure, mm Hg	78±6	79±6	0.19	0.22
Pulse pressure, mm Hg	40±7	39±7	0.13	-0.25
Stroke volume, mL	91±17	90±18	0.27	-0.22
Cardiac output, L/min	5.2±1.0	5.2±1.0	0.74	-0.05
Total peripheral resistance, mm Hg/L per min	15±2.9	16±3	0.39	0.15
Total vascular conductance, mL/min per mm Hg	67±12	66±12	0.41	-0.15
MSNA				
Burst frequency, bursts/min	26±10	31±12	<0.01	1.13
Total MSNA, AU/min	16±9	23±12	<0.01	1.70

Data presented as mean±SD. Cohen's d , representative of small (0.2–0.5), moderate (0.5–0.8), and large (>0.8) effect sizes. Hemodynamic and MSNA data obtained from 32 and 8 participants, respectively. AU indicates arbitrary units; LBNP, lower body negative pressure; MSNA, muscle sympathetic nerve activity.

stroke volume, cardiac output, and total peripheral resistance (or conductance) were not statistically different during low-level LBPP (all $P>0.05$; Table 2). However, systolic pressure, diastolic pressure, and mean arterial pressure were increased (all $P<0.05$; Cohen's $d=0.56$ –1.56) and pulse pressure reduced ($P=0.005$; Cohen's $d=-0.54$). MSNA burst frequency (-4%; $P=0.37$; Cohen's $d=-0.35$) and total MSNA (-7%; $P=0.89$; Cohen's $d=0.09$) were not statistically different during low-level LBPP. Similarly, central ($\Delta 0.0\pm 0.2$ m/s; $P=0.64$; Cohen's $d=0.07$) and whole body ($\Delta 0.0\pm 0.2$ m/s; $P=0.32$; Cohen's $d=-0.18$) PWV were not statistically different from baseline during LBPP (Figure 2). The responses of both cf-PWV and wb-PWV during LBPP were not impacted by pressure stimulus order (both $P>0.05$).

Discussion

Our study sought to provide proof-of-principle that modulation of peripheral sympathetic outflow could alter central and wb-PWV independent of a change in arterial pressure. Using the

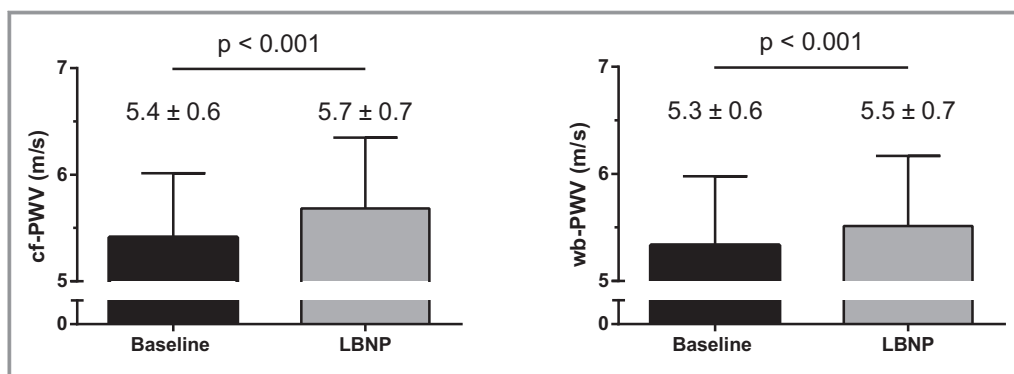


Figure 1. The effects of low-level lower body negative pressure (LBNP) on carotid-femoral pulse wave velocity (cf-PWV; left side) and whole-body pulse wave velocity (wb-PWV; right side).

model of low-level lower body pressure, we confirmed that LBNP did not alter arterial pressure but increased both MSNA and PWV (central and whole body). In contrast to our hypothesis, low-level LBPP caused small alterations in arterial pressure and failed to alter MSNA or PWV. Given that prior studies have failed to control experimentally the confounding effects of altered distending or pulsatile blood pressure on PWV, the present results address a key knowledge gap and demonstrate that acute increases in sympathetic activity can increase independently both central and whole body arterial stiffness.

Prior attempts to delineate the relationship between sympathetic activity and arterial stiffness have utilized experimental models that elicit parallel changes in vasoconstrictor outflow and blood pressure.^{24–30,42} For example, in 8 males the application of LBNP at -80 mm Hg or pre-syncope

threshold (group mean: -68 mm Hg) resulted in marked increases in cf-PWV of ≈ 2.5 m/s, which related strongly to increases in low-frequency power of systolic blood pressure,²⁶ an indirect estimate of peripheral sympathetic outflow.⁴³ However, although mean arterial pressure was unchanged during LBNP, this study noted trends for reductions in systolic blood pressure and failed to report pulse pressure changes,²⁶ the strongest correlate of central PWV.^{10,11} An examination of LBNP at 50% of maximum noted increases in cf-PWV of 0.7 m/s, but these failed to reach statistical significance, most likely because of the small sample size. More recently, Mäki-Petäjä and colleagues²⁹ argued against a role of the sympathetic nervous system in modulating cf-PWV based primarily on the observations that (1) acute pharmacological ganglion blockade did not alter cf-PWV compared with a saline condition in 8 participants; and (2) isometric handgrip

Table 2. Hemodynamic and MSNA Measurements at Baseline and During Low-Level LBPP

	Baseline	LBPP	P Value	Cohen's d
Heart rate, bpm	56±8	56±8	0.95	0.07
Systolic blood pressure, mm Hg	105±8	107±9	<0.001	0.56
Diastolic blood pressure, mm Hg	65±6	69±7	<0.001	1.56
Mean arterial pressure, mm Hg	78±6	82±7	<0.001	1.47
Pulse pressure, mm Hg	41±7	39±7	0.01	-0.54
Stroke volume, mL	91±17	89±18	0.08	-0.32
Cardiac output, L/min	5.1±1.2	5.1±1.1	0.77	0.07
Total peripheral resistance, mm Hg/L per min	16±5	17±4	0.76	0.05
Total vascular conductance, mL/min per mm Hg	65±15	63±13	0.27	-0.20
MSNA				
Burst frequency, bursts/min	23±11	22±11	0.37	-0.35
Total MSNA, AU/min	15±11	14±12	0.89	0.09

Data presented as mean±SD. Cohen's d, representative of small (0.2–0.5), moderate (0.5–0.8), and large (>0.8) effect sizes. Hemodynamic and MSNA data obtained from 32 and 8 participants, respectively. AU indicates arbitrary units; LBPP, lower body positive pressure; MSNA, muscle sympathetic nerve activity.

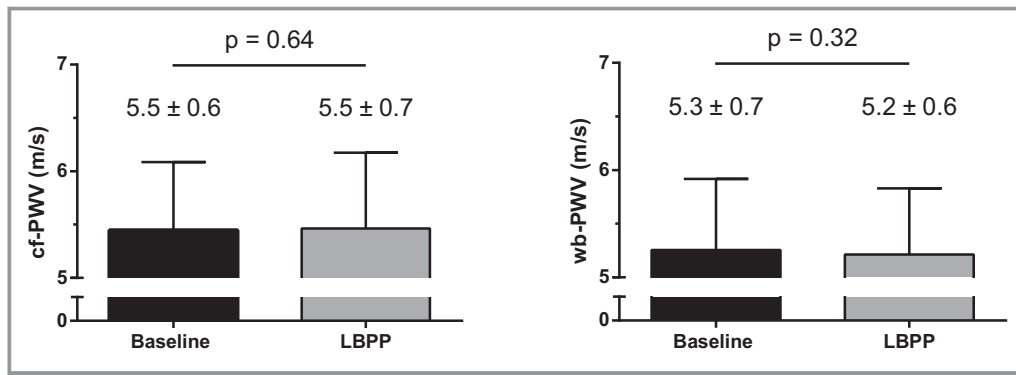


Figure 2. The effects of low-level lower body positive pressure (LBPP) on carotid-femoral pulse wave velocity (cf-PWV; left side) and whole-body pulse wave velocity (wb-PWV; right side).

exercise failed to modulate cf-PWV after statistical adjustment for the change in mean arterial pressure in 12 participants. However, the interpretations of this study are confounded by a number of important factors. First, the bolus dose of pentolinium used to elicit autonomic blockade was determined by changes in heart rate variability and likely had only small effects on the peripheral sympathetic outflow, as evidenced by the absence of a fall in total peripheral resistance and a rise in mean arterial pressure.²⁹ Confirmed complete ganglion blockade with trimethaphan in a similar-aged sample reduced mean arterial pressure by 9 mm Hg.³⁰ Second, the time course of cf-PWV measurements during supine isometric handgrip were not reported, though increases in peripheral sympathetic outflow are associated with activation of the muscle metaboreflex, which occurs >1 to 2 minutes of 30% maximal voluntary contraction.⁴⁴ Harvey and colleagues³⁰ also reported that cf-PWV was decreased in postmenopausal but not younger women during complete ganglionic blockade, though these changes were abolished with statistical adjustment for reductions in mean arterial pressure. Each of these observations is confounded by the fact that distending or pulsatile pressure can impact measures of PWV^{10,11}; however, noting a primary role of blood pressure on measures of vascular stiffness does not also preclude a lesser independent role of peripheral sympathetic activation that may be obscured by the experimental designs and limited sample sizes. Finally, each of the prior studies also reported differences in heart rate, which may also impact PWV measurements.⁴⁵

In agreement with past observations,^{31–33} the application of low-level LBNP in our larger cohort of participants had no impact on heart rate, blood pressure, stroke volume, cardiac output, or total peripheral resistance. In our subset of participants undergoing microneurography, these results were paralleled by increases in both MSNA burst frequency and total MSNA, of a similar magnitude reported previously.³² These results confirm that our model was able to increase

peripheral sympathetic outflow without altering blood pressure; simultaneously both cf-PWV and wb-PWV demonstrated small but consistent increases during LBNP. To ensure that the 0.3 m/s increase in cf-PWV was not the result of random variation, we calculated the baseline typical error of measurement and classified participants as responders or nonresponders. Based on this classification, we noted that 88% of participants (n=28) experienced an increase in cf-PWV. For context, a 1 m/s increase in cf-PWV has been estimated to increase the risk of total cardiovascular events, cardiovascular mortality, and all-cause mortality by 10%.³

The present study also aimed to test the effects of reducing sympathetic outflow on PWV. However, in contrast to our hypothesis, low-level LBPP increased mean arterial pressure and decreased pulse pressure without altering MSNA or PWV. The difference in blood pressure responses between the pressure stimuli may highlight the critical need to maintain appropriate perfusion pressure in the face of blood loss (LBNP) but the benefit of increasing venous return and perfusion pressure (LBPP) during conditions such as exercise. Surprisingly, PWV did not change during LBPP despite the acknowledged pressure dependency.^{8–11} We speculate that this could be the result of divergent effects of LBPP on mean blood pressure (distending) and pulse pressure (pulsatile) responses, or alternatively, that the small magnitude (≤ 4 mm Hg) changes in blood pressure are not sufficient to evoke detectable changes in PWV. With respect to sympathetic outflow, cardiopulmonary baroreceptor loading has been reported to elicit smaller reflex modulations in MSNA compared with cardiopulmonary unloading.³⁴ Whether a similar hysteresis exists with respect to the interaction of peripheral sympathetic activity on PWV is unknown, but may explain prior null findings under ganglion blockade in young participants.^{29,30} It should be noted that previous studies demonstrating reductions in MSNA with cardiopulmonary loading have primarily used +10 mm Hg LBPP,^{46,47} slightly higher than our pressure of +7 mm Hg. Nonetheless, LBPP

may serve as an internal control given that blood pressure was altered without changes in either sympathetic activity or PWV.

The observation that peripheral sympathetic activation can exert pressure-independent effects on PWV supports an important role for targeting central sympathetic discharge in clinical populations with increased aortic stiffness (eg, hypertension, heart failure, etc⁴⁸). However, strategies to reduce central sympathetic outflow, such as exercise training^{49,50} and renal denervation,^{51,52} have reported reductions in both blood pressure and central PWV, making it again difficult to disentangle the roles of neural and hemodynamic modulation on arterial stiffness.

We acknowledge several considerations. First, our sample consisted of young healthy participants and may not be translatable to older or disease populations. Sympathetic activity demonstrates age-related increases at rest¹⁶ and activation is accentuated during cardiopulmonary baroreflex unloading,⁵³ though the latter is paralleled by an attenuated vasoconstrictor response.⁵³ Second, we assessed blood pressure changes in the brachial artery, and these values might differ from central aortic pressure during LBNP or LBPP. Prior work using ganglion blockade has noted changes in central blood pressure³⁰; however, the relative changes were comparable between brachial and central blood pressure. In the present study, no changes in brachial blood pressure were observed during LBNP. Third, we confirmed sympathetic responses in a subset of participants using microneurographic assessments of MSNA. However, this direct measure of central sympathetic outflow to skeletal muscle vasculature may not be generalizable to other vascular beds. Finally, our study tested the reflex response to changes in peripheral vasoconstrictor outflow, not the tonic effects of sympathetic overactivation.

In conclusion, the present study provides support that modest increases in peripheral sympathetic activity, independent of a change in blood pressure or heart rate, can evoke acute increases in central and whole-body measures of arterial stiffness in young healthy participants. These findings address the limitation of prior models, which caused parallel changes in sympathetic activity and blood pressure. The independent role of acute sympathetic activation at higher intensities, or tonic elevations, requires further research. Applying these results, therapeutically targeting central sympathetic outflow may be beneficial to reduce the clinical risks associated with elevated cf-PWV.

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Disclosures

None.

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