Arterial Stiffness Can Be Modulated by Pressure-Independent Mechanisms in Hypertension

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Background—Effects of short-term interventions on large-artery stiffness assessed by pulse wave velocity (PWV) have mainly been explained by concomitant changes in blood pressure (BP). However, lower body negative pressure, which increases sympathetic activity and has other hemodynamic effects, has a specific effect on PWV in healthy volunteers.

Methods and Results—We examined effects of lower-limb venous occlusion (LVO), a similar intervention to lower-body negative pressure that reduces BP but increases sympathetic activity and device-guided breathing (DGB), which reduces both BP and sympathetic activity, on PWV in patients with essential hypertension (n=70 after LVO, n=45 after DGB and LVO in random order). The short-acting calcium channel antagonist nifedipine was used as a control for changes in BP. LVO produced a small but significant reduction in mean arterial pressure of 1.8 (95% CI 0.3–3.4) mm Hg. Despite this, aortic and carotid-femoral PWV increased during LVO by 0.8 (0.2–1.4) m/s and 0.7 (0.3–1.05) m/s, respectively. DGB reduced PWV by 1.2 (0.9–1.4) m/s, to a greater extent than did nifedipine 10 mg (reduction of 0.7 [0.1–1.3] m/s, *P*<0.05 compared with reduction during DGB). This occurred despite a greater decrease in BP with nifedipine compared with DGB.

Conclusions—Arterial stiffness can be modulated independently of BP over the short term. The mechanism could involve alterations in sympathetic activity or other as yet uncharacterized effects of LVO and DGB. (J Am Heart Assoc. 2019;8:e012601. DOI: 10.1161/JAHA.119.012601.)

Key Words: autonomic nervous system • high blood pressure • hypertension • pulse wave velocity • stiffness

Aortic and large artery stiffness is a major determinant of the pulsatile component of blood pressure (BP) and of cardiovascular risk.1–3 It is determined by an interplay between the steady-state component of BP (mean arterial blood pressure, MAP) that acts to distend the arterial wall, and properties of the wall that determine its stress–strain relationship.4 This, in turn, is thought to relate mainly to the mechanical properties of the extracellular matrix rather than being influenced by the tone of vascular smooth muscle.5 Vascular tone does influence arterial stiffness in muscular arteries6–9 (where it can be assessed independently of MAP) but its influence is difficult to assess in the aorta because interventions to alter vascular tone usually have systemic effects on MAP. Previous studies have reported conflicting results regarding a possible BP-independent role of the autonomic nervous system in the regulation of arterial stiffness.10–15 The interpretation of these studies has been limited by concurrent change in BP which, in almost all cases, has been in the same direction as the change in arterial stiffness. In the present study, we examined the effects of interventions that activate and deactivate the sympathetic nervous system on aortic and large artery pulse wave velocity (PWV) in patients with essential hypertension. We used lower-limb venous occlusion (LVO) that causes reflex sympathetic activation (similarly to low-level lower-body negative pressure16), device-guided breathing (DGB) to reduce sympathetic activity (SA),17 and a calcium channel blocker that acts predominantly on the microvasculature to provide a control for change in MAP. These interventions were expected to reduce BP but to have differing effects on PWV that would allow a specific (BP-independent) effect on PWV to be elicited.

Methods

Study Population

Anonymized individual patient data used in this study will be made available to academic investigators through the
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Clinical Perspective

What Is New?
• Stiffness of large elastic arteries can be modified independently of blood pressure in subjects with hypertension.
• The mechanism could involve alterations in sympathetic activity regulating vascular smooth muscle tone in large elastic arteries.

What Are the Clinical Implications?
• Dissociation of arterial stiffness and blood pressure has potential implications for therapeutics since interventions that directly reduce sympathetic activity may have additional benefits to the extent that would be achieved by the reduction in blood pressure.

corresponding authors. Participants were consecutively consenting subjects attending the hypertension clinics at Guy’s and St Thomas’ Hospital over the period August 2017 to December 2018 who were invited to take part in 1 of the 2 studies described below. Hypertension was diagnosed on the basis of previous treatment and/or daytime systolic ambulatory BP (or home BP averaged ≥7 days) of >135 mm Hg systolic or >85 mm Hg diastolic, according to current guidelines. Pregnant women were excluded from the study, as were those in whom the clinical history or investigations suggested a presence of secondary hypertension. Patients with moderate or severe valvular disease and/or those with sustained nonsinus arrhythmias were also excluded. The study was approved by the London Westminster Research Ethics Committee, and written informed consent was obtained from all patients. The following hemodynamic measurements were obtained in addition to measurement of height, weight, and routine biochemistry.

BP and Pulse Wave Analysis
Participants were asked to abstain from caffeine, alcohol, and strenuous exercise for at least 24 hours before hemodynamic measurements, which were conducted in a temperature- and light-controlled laboratory following voiding. After 15 minutes of supine rest, BP and heart rate (HR) were recorded in the brachial artery using a validated oscillometric technique (HEM-705CP, Omron Corp, Kyoto, Japan). The average of 3 consecutives readings of systolic BP (SBP) and diastolic BP (DBP) was used for the analysis. Pulse wave analysis of the radial artery (SphygmoCor, AtCor Medical, Sydney, Australia) was performed for estimation of the central aortic pressure from the radial artery using the SphygmoCor generalized transfer function, with calibration from brachial BP. Measurements were performed by a single operator in triplicate with an in-device quality rating ≥85% required for all the recordings, which were then averaged for analysis.

Pulse Wave Velocity
Aortic PWV (aPWV) was estimated with pulsed Doppler (Philips Epiq 7 ultrasound system, Koninklijke Philips N.V., Amsterdam, The Netherlands) by measuring the time taken by the pulse wave to travel along the thoracic aorta from the aortic arch to the abdominal aorta. Transit time was estimated by the difference between the R-wave of a simultaneously recorded ECG and the foot of the flow wave recorded at proximal and distal sites. The path length between the 2 insonated sites was estimated from surface markings (sternal notch to xiphoid process) and aoPWV calculated as the quotient of path length and transit time. Measurements were made by a single operator, and the average of 2 consecutive measurements was used for the analysis. Carotid–femoral pulse wave velocity (cfPWV) was measured from ECG-referenced carotid and femoral tonometric recordings obtained using the SphygmoCor device. Measurements were made by a single operator and the average of 2 consecutive measurements was used for the analysis.

Heart Rate Variability
HRV (Schiller Medilog AR12plus, United States) was assessed in the frequency domain as previously described. With the patient lying in the supine position, short-term recordings were performed after 15 minutes of rest and then repeated every 3 minutes. The spectral profile of human HRV contains 3 components, with frequencies at rest centered at 0.00 Hz (very low frequency), 0.10 Hz (LF=low frequency), and around the respiratory rate (HF=high frequency), respectively. HF and LF components are influenced by parasympathetic and SA, respectively, and the ratio of LF/HF is influenced by sympathetic relative to parasympathetic activity. However, it has been stressed by many authors that HRV and the LF/HF ratio is not a measure of SA.

Study Protocols

Study 1: Effects of LVO on BP and PWV
LVO is a novel technique developed to create an isolated reduction of preload within the physiological range using low-pressure thigh cuff inflation. Briefly, pneumatic leg cuffs are applied around the thighs and inflated to a supradiastolic, subsystolic brachial BP. This causes venous pooling in the legs with a decrease in cardiac output and reflex sympathetic activation but with only minimal effects on BP. Baseline measurements of BP, pulse wave analysis (PWA), and aPWV

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were obtained after 15 minutes of supine rest and repeated after 5 minutes of continuous cuff inflation (with cuffs inflated for a total of 10 minutes). In a subsample of subjects (n=23) cfPWV was also measured before and after LVO.

**Study 2: Comparative effects of LVO, DGB, and nifedipine on BP, HRV, and PWV**

In this study we compared effects of LVO and DGB on cfPWV. PWV was measured over the carotid-femoral route rather than over the thoracic aorta because insonation of the abdominal aorta tends to disturb and is confounded by the deeper breathing induced by DGB. Measurements of BP, PWA, cfPWV, and HRV were performed at baseline and after LVO (as described in study 1) and DGB (Resperate, InterCure Ltd., Lod, Israel) with these 2 interventions performed in random order. The DGB device consists of a respiration sensor and headphones, which provides feedback to the patient. During a session of DGB, the breathing rate and pattern are analyzed and feedback sounds generated to allow the expiratory phase of each breath to be prolonged and respiratory rate to be reduced to <10 breaths/min. This produces an immediate suppression of muscle sympathetic nerve activity and has a modest effect on lowering BP. In a subsample of participants (n=19), after performing DGB and LVO as previously described, nifedipine 10 mg was administered orally. With the patient still lying in the supine position, hemodynamic measurements were repeated over a period of 30 to 60 minutes after administration of nifedipine when its effects were close to maximal. Nifedipine is a short-acting dihydropyridine calcium antagonist that reduces BP and causes a reflex activation of muscle sympathetic nerve activity.

**Sample Size and Statistics**

Sample size was estimated from previous studies on the repeatability of PWV. A sample size of n>70 for study 1 was chosen to provide >90% power for a type I error rate 0.05 to detect a change in aoPWV >0.5 m/s. Sample size for study 2 (n=40) was chosen to give similar power to detect a difference in PWV between interventions of 0.5 m/s (the within-subject SD of cfPWV being less than that of aoPWV). Statistical analysis was performed using SPSS24 (IBM). Subject characteristics and results are expressed as mean±SD or mean (95% CI). Differences in means before and after interventions were analyzed using Student’s paired t test for normally distributed variables, or Wilcoxon rank sum test for not normally distributed variables. P<0.05 was considered statistically significant and all tests were 2-tailed. Categorical variables were compared by χ² test. Pearson’s product-moment coefficient was used to explore correlations between variables.

**Table 1. Characteristics of the Study Population**

| Variable                  | Study 1 (n=70) | Study 2 (n=45) |
|---------------------------|----------------|----------------|
| Age, y                    | 45.5±12.9      | 46.8±12.64     |
| Sex (% male)              | 61.4           | 62.2           |
| Race                      |                |                |
| White (%)                 | 39.7           | 35.6           |
| Black, %                  | 39.7           | 46.7           |
| Others, %                 | 20.6           | 17.8           |
| BMI, kg/m²                | 28.0±4.55      | 28.3±4.47      |
| Diabetes mellitus, %      | 7.1            | 6.8            |
| Dyslipidemia, %           | 22.9           | 22.7           |
| CV event, %               | 5.7            | 6.8            |
| Creatinine, mmol/L        | 97.87±44.80    | 89.74±23.81    |
| HbA1c, mmol/mol           | 39.72±8.21     | 40.33±12.56    |
| Total cholesterol, mmol/L | 4.83±0.85      | 4.75±1.19      |
| Drug treatment, %         | 62.9           | 62.2           |
| ACE, ARB, %               | 37.1           | 31.1           |
| CCB, %                    | 34.3           | 40             |
| BB, %                     | 10             | 11.1           |
| Diuretic, %               | 21.4           | 28.9           |
| Doxazosin, %              | 5.7            | 11.1           |
| Other treatment, %        | 5.7            | 6.7            |

Values are means±SD or percentages. ACE indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; BMI, body mass index; CCB, calcium channel blocker; CV event, previous cardiovascular event; HbA1c, glycosylated hemoglobin.

**Table 2. Study 1: Effects of LVO on Hemodynamics and Pulse Wave Velocity (n=70)**

| Variable          | Baseline | LVO      | P Value |
|-------------------|----------|----------|---------|
| SBP, mm Hg        | 142.15±17.05 | 138.06±17.04 | <0.001  |
| DBP, mm Hg        | 89.34±12.84  | 89.85±12.54  | 0.380   |
| HR, bpm           | 78.16±21.88  | 77.29±21.30  | 0.221   |
| cSBP, mm Hg       | 124.52±19.09 | 121.30±17.54 | 0.001   |
| cDBP, mm Hg       | 92.26±14.67  | 92.15±14.21  | 0.883   |
| MAP, mm Hg        | 103.97±16.67 | 102.14±15.68 | 0.021   |
| cAP, mm Hg        | 8.41±6.68    | 6.55±6.06    | 0.001   |
| cPP, mm Hg        | 38.36±10.32  | 34.47±8.89   | <0.001  |
| cAIx, %           | 20.47±13.71  | 17.95±14.49  | 0.036   |
| aoPWV, m/s        | 7.23±2.29    | 8.08±3.66    | 0.005   |
| cfPWV, m/s        | 9.18±1.98    | 9.87±2.60    | 0.001   |

aoPWV indicates aortic pulse wave velocity; bpm, beats per minute; cAIx, central augmentation index; cAP, central augmentation pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cPWV, carotid-femoral pulse wave velocity; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVO, lower-limb venous occlusion; MAP, mean arterial pressure; SBP, systolic blood pressure.
Results

Study 1: Effects of LVO on BP and PWV

Characteristics of hypertensive patients (n=70) are reported in Table 1. Patients were predominantly young to middle-aged men and women, most of whom were overweight, and a relatively high proportion were of black ethnicity in line with the demographics of referrals to the hypertension service in southeast London. Forty-four patients were on pharmacological treatment with 1 or more antihypertensive drugs. LVO had no significant effect on HR or DBP but produced a small but significant decrease in SBP of 3.4 (95% CI 1.6–5.2) mm Hg as well as a reduction in MAP (reduction of 1.8 [0.3–3.4] mm Hg, central SBP and central pulse pressure (reduction of 3.9 [2.1–5.7] mm Hg, Table 2). Despite the reduction in MAP, aoPWV increased during LVO by 0.8 (0.3–1.4) m/s. A similar increase of 0.7 (0.3–1.0) m/s was seen in cfPWV. The dissociation of change in cfPWV with BP components applied not only to MAP but to peripheral and central SBP.

Study 2: Effects of LVO and DGB on BP, HRV, and cfPWV

Forty-five patients were recruited in study 2, and their characteristics were similar to those in study 1 (Table 1). As in study 1, LVO had no significant effect on HR or DBP but produced small but significant decreases in SBP and MAP of 3.9 (2.1–5.6) mm Hg and 1.3 (0.2–2.5) mm Hg, respectively (Table 3, Figure). cfPWV increased during LVO to a similar extent as in study 1: by 1.0 (0.7–1.3) m/s. HRV analysis showed a significant increase in the log ratio LF/HF of 0.14 (0.09–0.18) during LVO. Compared with LVO, DGB produced a more marked decrease in BP with reductions in SBP and MAP of 10.5 (8.6–12.4) mm Hg and 6.8 (5.4–8.2) mm Hg, respectively, as well as significant reductions in HR and DBP of 3.9 (2.2–5.7) beats per minute and 4.7 (3.3–6.1) mm Hg, respectively. Log LF/HF decreased by 0.12 (0.06–0.17). cfPWV was reduced by 1.2 (0.9–1.4) m/s during DGB. When comparing effects of DGB with nifedipine (n=19), nifedipine produced a greater reduction in MAP (reduction of 13.4 [10.2–17.7] mm Hg, \( P=0.009 \) compared with reduction during DGB) with a tendency for log LF/HF to increase rather than decrease so that the change in log LF/HF after nifedipine was significantly greater than that during DGB \( (P=0.05, \text{ Table 3}). \) Despite a comparatively greater reduction in BP (MAP, SBP, and cSBP) by nifedipine, the decrease in cfPWV was less than that observed with DGB (0.5 [0.1–1.0] m/s; \( P=0.022 \) compared with reduction during DGB, Figure).

Discussion

This is the first study, as far as we are aware, to show a dissociation between change in PWV and change in BP in

| Variable | Baseline | LVO | DGB | Nifedipine |
|----------|----------|-----|-----|------------|
| All subjects (n=45) |
| SBP, mm Hg | 146.36±16.75 | 142.49±15.89* | 135.82±15.28* | ... |
| DBP, mm Hg | 88.38±9.53 | 89.04±10.05 | 83.67±9.49* | ... |
| HR, bpm | 70.18±12.48 | 69.51±12.13 | 66.22±11.88* | ... |
| MAP, mm Hg | 108.41±11.08 | 107.07±11.78 | 101.61±10.82* | ... |
| cSBP, mm Hg | 133.09±16.10 | 129.55±15.22* | 124.43±15.31* | ... |
| cfPWV, m/s | 10.01±2.00 | 11.01±2.32† | 8.83±1.71* | ... |
| HRV (logLF/HF) | 0.31±0.28 | 0.44±0.27* | 0.18±0.30* | ... |
| Subsample receiving nifedipine (n=19) |
| SBP, mm Hg | 150.44±12.01 | 146.06±12.56* | 138.17±11.10* | 133.17±11.80* |
| DBP, mm Hg | 89.83±8.77 | 90.11±8.91 | 84.39±9.15* | 78.83±9.23* |
| HR, bpm | 65.89±11.15 | 65.50±11.07 | 62.33±11.95* | 75.06±12.58* |
| MAP, mm Hg | 110.78±9.00 | 109.22±9.56 | 103.00±8.41* | 97.33±9.70* |
| cSBP, mm Hg | 136.48±10.72 | 131.26±11.0* | 128.11±10.77* | 118.57±11.08* |
| cfPWV, m/s | 10.33±2.38 | 11.29±2.36* | 9.04±1.84* | 9.59±2.01† |
| HRV (logLF/HF) | 0.35±0.29 | 0.51±0.28* | 0.25±0.37* | 0.42±0.33 |

bpm indicates beats per minute; cfPWV, carotid-femoral pulse wave velocity; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; DGB, device-guided breathing; HF, high frequency; HR, heart rate; HRV, heart rate variability; LF, low frequency; LVO, lower-limb venous occlusion; MAP, mean arterial pressure; SBP, systolic blood pressure.

* \( P<0.01 \) compared with baseline.
† \( P=0.05 \) compared with baseline.
subjects with hypertension. Most acute interventions that modulate cfPWV can be explained by their effects on MAP, influencing distension of the arterial wall and hence loading or unloading stiffer elements within the wall. Lack of a specific effect on the wall has been attributed to the relatively small amount of vascular smooth muscle within the wall of large elastic arteries compared with muscular conduit arteries. This study by contrast demonstrates a clear dissociation between change in MAP and PWV during LVO, with an increase in PWV despite a decrease in MAP. The dissociation of change in cfPWV with BP components applied not only to MAP but to peripheral and central SBP. While the increase in PWV is modest, it is clinically significant and is equivalent to the change seen with age over a period of 5 to 10 years. Importantly, it is also seen when PWV is measured over the elastic aorta as well as over the carotid–femoral region, thus excluding an effect restricted only to more muscular regions of the carotid–femoral pathway. LVO had no significant effect on HR and decreased pulse pressure as well as MAP, effects that generally tend to reduce rather than increase PWV. One explanation for the increase in PWV with LVO is the well-recognized activation of SA produced by a reduction in venous return (as evidenced indirectly in the present study by change in HRV) acting to increase vascular smooth muscle tone.

Previous interventional studies have reported conflicting results regarding a possible BP-independent role of the autonomic nervous system in the regulation of arterial stiffness. A common limitation in most of these studies was, however, the confounding effects of altered distending or pulsatile BP. Our findings are in line with a recent study conducted in healthy normotensive subjects using lower-body negative pressure showing an increase in PWV despite no brachial BP change. Lower-body negative pressure had modest sympathoexcitatory effects confirmed by increases in muscle sympathetic nerve activity.

Further evidence in the present study to support a BP-independent effect on PWV is provided by the effects of DGB, an intervention that has short-term effects to reduce muscle sympathetic nerve activity. While the reduction in PWV seen during DGB could have been explained by the concurrent decrease in MAP, comparison with the effects of nifedipine largely excludes this possibility. Nifedipine produced a smaller decrease in PWV despite a larger drop in all BP components (Figure). These observations would be consistent with an effect on PWV mediated through modulation of SA, since nifedipine is known to cause a reflex increase in SA. Taken together, the effects of LVO and DGB demonstrate that cfPWV and aoPWV can be changed independently of BP, and that the mechanism of such dissociation could involve sympathetic activation influencing the tone of smooth muscle in the aortic wall.

There are several important consequences of these observations. Previous studies have examined the pressure dependence of aoPWV and cfPWV by modulating BP, under physiological conditions of an intact autonomic nervous system, and may have underestimated the true pressure dependence of PWV because a drop in BP will tend to cause a reflex activation of SA and hence attenuate the fall in PWV while a rise in BP will do the opposite. This will not disrupt the continuous relationship between PWV and MAP, but will alter the slope of this relationship; a dissociation between PWV and MAP will only be apparent for interventions such as LVO that have opposing effects on SA and BP.

While the role of SA in mediating the BP-independent changes in PWV remains speculative, such an influence of SA on PWV would have implications for therapeutics. Beneficial effects of antihypertensive drugs that cause reflex sympathetically mediated activation could be offset by a rise in PWV as well as by other mechanisms. Conversely, interventions that directly
reduce SA may have additional benefits to reduce PWV to a greater extent than would be achieved by the reduction in MAP. It is notable that 2 studies that have examined the effects of peripheral α-adrenergic receptor blockade have demonstrated a BP-independent reduction in measures of PWV. While α-adrenergic receptor blockade may not be effective in reducing adverse outcomes when compared with other antihypertensive drugs, this may be because of unopposed β-adrenergic activation, and combined α- and β-blockade is thought to confer increased protection. In studies of renal denervation, reduction of PWV to a greater extent than can be explained by BP has been observed, which would be consistent with a medium-term effect of SA on PWV.

Limitations

There are several important limitations to our study. We examined hypertensive patients, the majority of whom were on treatment; further studies will be required to determine whether the effects of LVO and DGB differ between normotensive and hypertensive subjects and according to hypertensive phenotype. Although a change in SA provides a potential explanation for our findings of a dissociation of cfPWV with BP after LVO and DGB, further interventional studies will be required to establish this with certainty and to distinguish whether these effects are directly related to action on vascular smooth muscle or are mediated by other hemodynamic changes or other mechanisms that we did not capture in the present study. Reduction in cardiac preload, for example, leads to a reduction in stroke volume and while this would theoretically be expected to decrease rather than increase cfPWV, we are not aware of any studies that have examined the influence of stroke volume directly. DGB could have effects that are mediated through alterations in arterial blood gases, although we are not aware of any studies that have demonstrated such an effect. HRV is an indirect measure of SA and is influenced by other factors including vagal tone and respiratory rate, and thus may not reflect sympathetic outflow. However, previous studies have shown that muscle sympathetic nerve activity, a more direct measure of SA, changes in parallel with the changes in HRV that we observed in the present study. Lastly, we examined only the immediate effects of sympathetic modulation. Long-term effects will require further study.

Conclusions

Arterial stiffness can be modulated independently of BP over the short term, possibly through alterations in SA. Interventional studies to examine effects of a reduction in SA on PWV above those expected by a reduction in BP alone are required to confirm the mechanism of BP-independent modulation of PWV.

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Disclosures

None.

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