Vessels

Altered Dependence of Aortic Pulse Wave Velocity on Transmural Pressure in Hypertension Revealing Structural Change in the Aortic Wall

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Abstract—Aortic pulse wave velocity (aPWV), a major prognostic indicator of cardiovascular events, may be augmented in hypertension as a result of the aorta being stretched by a higher distending blood pressure or by a structural change. We used a novel technique to modulate intrathoracic pressure and thus aortic transmural pressure (TMP) to examine the variation of intrathoracic aPWV with TMP in hypertensive (n=20; mean±SD age, 52.1±15.3 years; blood pressure, 159.6±21.2/92.0±15.9 mm Hg) and normotensive (n=20; age, 55.5±11.1 years; blood pressure, 124.5±11.9/72.6±9.1 mm Hg) subjects. aPWV was measured using dual Doppler probes to insonate the right brachiocephalic artery and aorta at the level of the diaphragm. Resting aPWV was greater in hypertensive compared with normotensive subjects (897±50 cm/s versus 784±43 cm/s; $P<0.05$). aPWV was equal in hypertensive and normotensive subjects when measured at a TMP of 96 mm Hg. However, dependence of aPWV on TMP in normotensive subjects was greater than that in hypertensive subjects (9.6±1.6 versus 3.8±0.7 cm/s per mm Hg increase in TMP, respectively, means±SEM; $P<0.01$). This experimental behavior was best explained by a theoretical model incorporating strain-induced recruitment of stiffer fibers in normotensive subjects and fully recruited stiffer fibers in hypertensive subjects. These results explain previous contradictory findings with respect to isobaric aPWV in hypertensive compared with normotensive subjects. They suggest that hypertension is associated with a profound change in aortic wall mechanical properties possibly because of destruction of elastin leading to less strain-induced stiffening and predisposition to aortic dissection. (*Hypertension.* **2015;65:362-369. DOI: 10.1161/HYPERTENSIONAHA.114.04370.**)

Key Words: aortic dissection ■ collagen ■ elastin ■ pulse wave analysis ■ vascular stiffness

Stiffening of the aorta, a ubiquitous feature of cardiovascular ageing, imposing adverse loading on the left ventricle and generating high pulse pressure, predisposes to cardiovascular events independent of traditional risk factors.[1,2] The determinants of aortic stiffening are, however, poorly understood. Aortic pulse wave velocity (aPWV, the measure of aortic stiffening with most prognostic impact) is only weakly, if at all, associated with traditional risk factors for cardiovascular disease other than age and blood pressure.[3,4] By contrast, aPWV is closely associated with concurrent levels of blood pressure[5] implicating hypertension in the etiology of aortic stiffening. However, it is unclear whether the relation of aPWV to blood pressure is simply because of the aorta becoming stiffer as it is stretched by a higher transmural distending pressure (TMP, usually equal to intra-aortic blood pressure)[6] or whether it results from a structural change in the aortic wall associated with and contributing to a sustained elevation in blood pressure (ie, hypertension). Previous attempts to address this question by obtaining indirect estimates of isobaric stiffness have yielded conflicting results.[7–10] However, isobaric stiffness does seem to be of prognostic significance.[11] In the present study, we have exploited a novel technique to modulate TMP independent of blood pressure by controlled variation of intrathoracic pressure (ITP) around the adventitial surface of the aorta. We used this to examine the relation of aPWV to TMP in normotensive and hypertensive subjects, reasoning that if aPWV in hypertension is because of a higher TMP, then aPWV in hypertensive subjects would equal that in normotensive subjects when measured at the same TMP. We then used a theoretical model to examine whether aPWV-TMP relationships may be explained by recruitment of collagen fibers in an elastin/collagen matrix when the aorta is distended by increased TMP.

Methods

Subjects

Patients with essential hypertension were recruited from the hypertension clinic at Guy's and St Thomas' Hospital. Hypertension was diagnosed as an office blood pressure >140/90 mm Hg on ≥3 occasions and ambulatory blood pressure >130/85 mm Hg. Patients on treatment for hypertension were included if office blood pressure on treatment was >140/90 mm Hg. Exclusion criterion included intercurrent illness, pregnancy, significant systemic disease other than mild hypertensive nephropathy, echocardiographic evidence of left ventricular ejection fraction <50%, and rhythm other than sinus rhythm. Subjects were also excluded if high-quality Doppler waves could not be recorded from the aorta. Healthy volunteers on no regular medication of a similar age and sex distribution to hypertensive subjects were recruited by advertisement from the local community. The study was approved by the London Westminster Research Ethics Committee, and written informed consents were obtained from all participants. Subject characteristics are summarized in the Table. Drug treatment in hypertensive subjects comprised angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists (5/20 subjects), calcium channel antagonists (7/20), diuretics (4/20), β-adrenergic receptor antagonists (3/20), and α-adrenergic receptor antagonists (2/20).

Doppler Ultrasound Measurement of Intrathoracic aPWV During Modulation of ITP

aPWV was measured using a dual probe, continuous wave, Doppler ultrasound system developed at our institute. Four megahertz and 2 MHz bidirectional probes (VP4-HS and OP2-HS; Huntleigh Healthcare Ltd, Cardiff, UK) were used to insonate the right brachiocephalic artery and aorta at the level of the diaphragm (Figure 1). Beat-to-beat transit time between the 2 sites was measured as described below, path length estimated from the distance from sternal notch to xiphisternum and beat-to-beat aPWV calculated from path length/transit time.

Mouth pressure (which under conditions of zero flow equals intrapulmonary pressure) was varied by asking subjects to perform Valsalva and Mueller maneuvers (Figure 1) with their mouth sealed around a mouthpiece (Spiroguard, Air Safety Limited, Morecambe, UK) connected to an occluded airway with a small leak, to ensure that mouth pressure during the maneuver was generated in the thoracic cavity. Mouth pressure was measured by a pressure sensor (Omega, Irlam, Manchester, UK) connected just proximal to the occluded airway.[12] Although ITP on the adventitial surface of the aorta differs by

a few mm Hg from intrapulmonary pressure because of the elastic recoil pressure of the lung, change in ITP at fixed lung volume is equal to that of intrapulmonary pressure.[13] Under conditions of zero flow, mean TMP across the intrathoracic aortic wall is thus closely approximated by the difference between mean intra-arterial pressure (MAP) and ITP as measured from mouth pressure. Mouth pressure was displayed on a video screen, allowing subjects to adapt inspiratory/expiratory effort to reach a target ITP.

Beat-to-beat MAP was measured using a servo-controlled Finometer finger photoplethysmographic system (Finometer MIDI; Finapres Medical Systems B.V., Amsterdam, The Netherlands), previously shown to track blood pressure accurately during Valsalva and Mueller maneuvers.[14,15] The Finometer system MAP was calibrated at intervals using an oscillometric blood pressure monitor (HBP-1300; Omron Healthcare Europe B.V., Hoofddorp, The Netherlands) at the brachial artery with an appropriate sized cuff placed on the right arm.

Test Protocol

Before the test, subjects were trained to perform Valsalva and Mueller maneuvers with ITP displayed on a monitor, providing visual feedback with which to practice the maneuvers. They were asked to gradually increase the magnitude of respiratory effort, and hence ITP, in an approximately linear fashion and then hold it at a pressure of 20 to 30 mm Hg (Figure 3). A gradual increase in ITP (rather than attempting a series of incremental steps) made it easier to track the aorta during the maneuver, particularly at the diaphragm, while providing measures of aortic blood velocity at both Doppler probe locations, with TMP varying over an approximately linear range of MAP±25 mm Hg. After training, 3 recordings of beat-to-beat aPWV and MAP were made at baseline during free breathing (when TMP was assumed equal to MAP) followed by 3 recordings during progressive Valsalva and Mueller maneuvers during which beat-to-beat aPWV, MAP, and ITP (and therefore TMP) were recorded simultaneously while supine. Recordings were repeated if the signal was lost at the level of the diaphragm because of the aorta moving during a maneuver. Each recording captured ≈1 minute of continuous data. Oscillometric blood pressure was measured at the beginning and end of each test. The Finapres recording was then calibrated according to a linear interpolation in time between these 2 points.

The maneuvers, notably Valsalva, tended to displace the descending aorta affecting the signal amplitude of the distal waveform, and some recordings were thus of higher quality than others. One of each of the 3 recordings (free breathing, Valsalva, and Mueller maneuvers) was therefore manually selected based on the amplitude and quality of the velocity signals by an observer blinded to the final results. This allowed an aPWV versus TMP profile to be compiled for each subject.

Signal Processing

Doppler ultrasound signals and pressure signals were acquired using an analog-to-digital conversion card (USB-6211; National Instruments, Austin, TX), and subsequent signal processing was done with software developed at our institute written in MATLAB (The MathWorks, Natick, MA). Successive discrete Fourier transforms were performed on 20-ms windows of the raw Doppler data (sampling frequency 8000 Hz) applied in a sliding sample fashion with 40% overlap of window length. A Hamming window filter was applied to each discrete window sample to minimize spectral leakage.[16] This approach optimized the trade-off between temporal resolution of velocity profiles and signal-to-noise ratio and provided a temporal resolution of 8 ms. Velocity waveforms were filtered with a Savitzky-Golay filter (which maintains high frequency components of the waveform) before identifying the foot of the waveform at end diastole using an early systolic least squares method to minimize transit time measurement error and variability.[17] TMP was obtained from the difference between MAP and ITP, and aPWV values averaged over 10 mm Hg ranges of TMP to provide an aPWV versus TMP profile for each subject and mean aPWV versus TMP profiles for the

Table.   Characteristics of Normotensive and Hypertensive Subjects

Measure	Normotensive	Hypertensive
Number (males)	20 (7)	20 (9)
Age, y	55.5±11.1	52.1±15.3
Height, cm	171.2±10.4	170.5±10.0
Weight, kg	66.4±12.7	77.3±15.2
SBP, mm Hg	124.5±11.9	159.6±21.2*
DBP, mm Hg	72.6±9.1	92.0±15.9*
MAP, mm Hg	89.9±8.6	114.6±16.8*
Total cholesterol, mmol/L	5.3±0.8	5.6±1.3
HDL cholesterol, mmol/L	1.8±0.6	1.6±0.4
Triglycerides, mmol/L	1.0±0.4	1.4±0.8

Values are means±SD. DBP indicates diastolic blood pressure; HDL, high density lipoprotein; MAP, mean arterial pressure; and SBP, systolic blood pressure.

*$P<0.0001$ compared with controls.
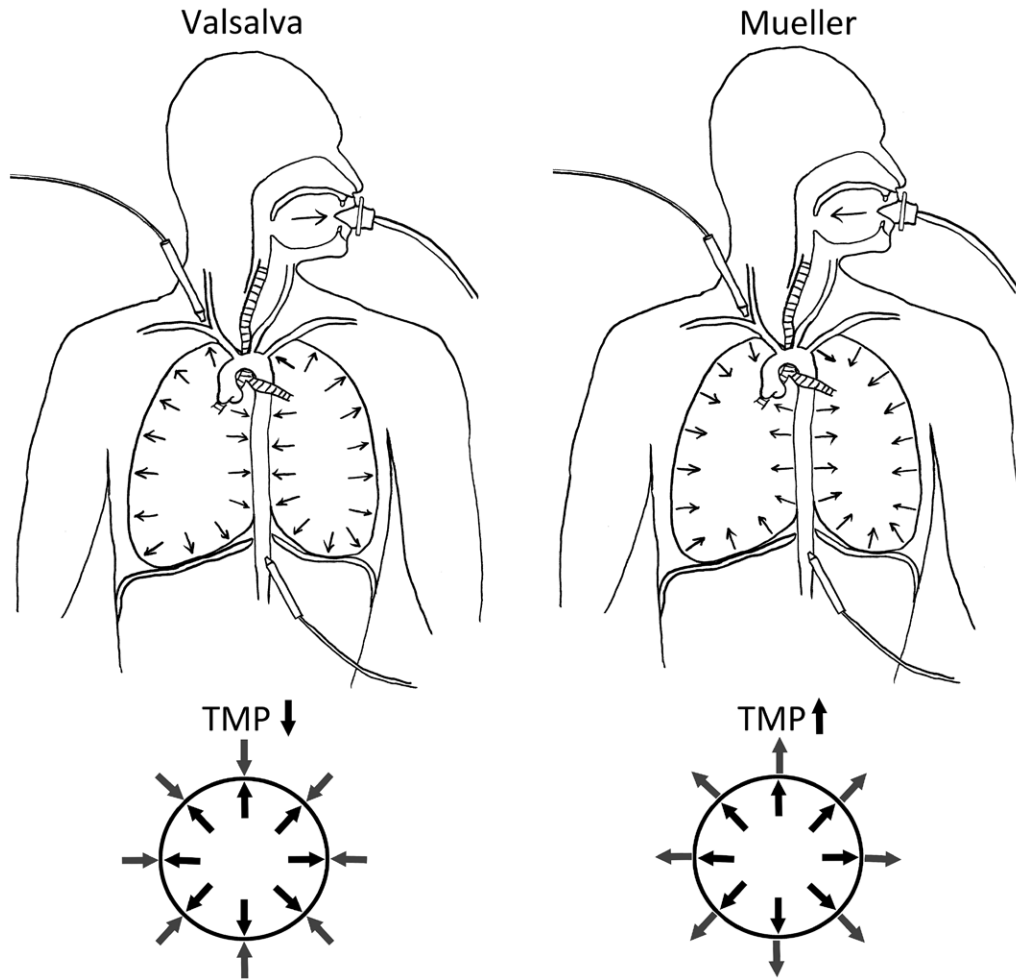
Figure 1. Valsalva (**left**) and Mueller (**right**) maneuvers where the subject exhales or inhales, respectively, against a mouthpiece to decrease or increase intrathoracic pressure (ITP), and thus the aortic transmural pressure (TMP). Also shown are the Doppler ultrasound probes and mouthpiece used to measure the ITP.

normotensive and hypertensive groups. Heart rate for each subject was averaged over the same 10 mm Hg ranges of TMP.

Statistical Methods

Subject characteristics are presented as means±SD and results as means±SEM. Variation of aPWV with TMP was assessed by a multiple regression model incorporating age, sex, hypertension (as a dummy variable), and an interaction between TMP and hypertension to test for differing aPWV versus TMP gradients in hypertensive and normotensive subjects. All results were adjusted for subject age. All analysis was performed in SPSS (version 19). All tests were 2-tailed, and $P<0.05$ was considered significant.

Theoretical Model

To explain observations in the clinical data, the relationship between aPWV and TMP was analyzed theoretically. This incorporated the classical stress-strain relationship applied to a thin-walled cylinder relating TMP to distension, then an elastic modulus model for aortic wall tissue, and finally the Bramwell-Hill equation to relate aPWV to mechanical properties. The following provides a brief description of the theoretical relationship between aPWV and TMP.

The hoop stress (σ) in the aortic wall caused by TMP induces an elastic strain (ε) according to,

$$\sigma = E\varepsilon, \tag{1}$$

where E is the Young modulus of the aortic wall (for a composite elastic and collagen or homogeneous elastic material). Applying this to a thin shell cylinder model,[18] the following relationship between TMP and aortic diameter Ø can be derived[19]:

$$\text{TMP} = \frac{8E_{\text{inc}}h(\varnothing - \varnothing_0)}{3\varnothing_0^2}, \tag{2}$$

where h is the wall thickness and $\varnothing_0$ is the unloaded diameter (*TMP* of 0).

Depending on the assumed structure of the aortic wall, either a composite nonlinear elastance (NLE) model or a linear elastance (LE) model may be assumed. The NLE model assumes that resistance to aortic wall strain is provided by elastin and incrementally recruited collagen fibers, whereas the LE model accommodates aortic wall strain by a homogeneous elastic tissue with a constant Young modulus.

In the NLE model, aortic stiffness (E) comprises the composite stiffness of the elastin/collagen in the media and intima. The stiffness of a 2-species composite material (E_{inc}) is evaluated as the area fraction–weighted sum of each species' stiffness.[20] Assuming homogeneity along the vessel length, this area fraction can be replaced by a through-thickness fraction,

$$E_{\text{inc}} = \frac{h_e}{h}E_e + \frac{h_c}{h}E_c = pE_e + (1-p)E_c, \tag{3}$$
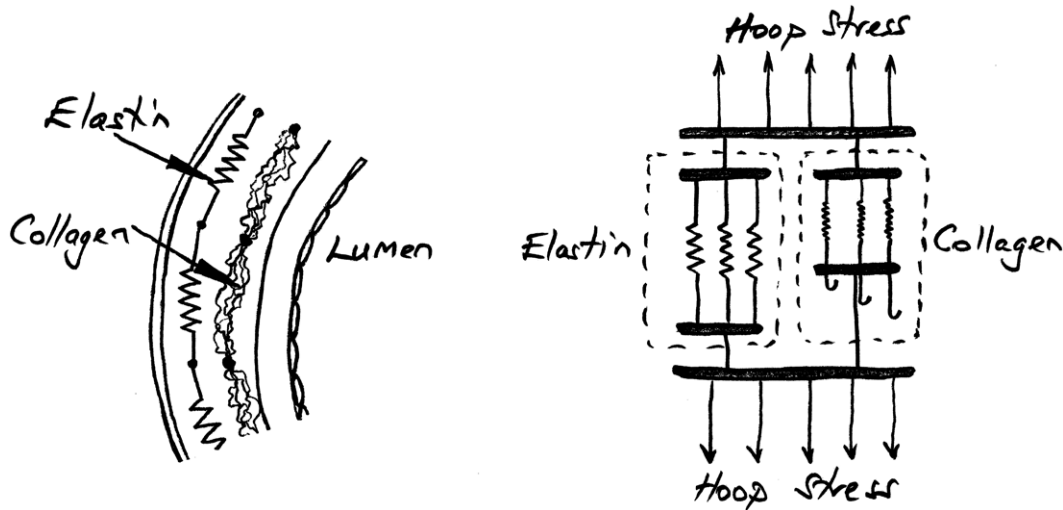
Figure 2. Parallel elastin/collagen models, where stiffness is governed by incrementally recruited collagen fibers as the aorta is stretched.

where h_e and h_c are the proportions of the effective cumulative thicknesses of elastin fibers and collagen fibers, respectively, divided by the thickness h (ie, $h_e + h_c = 1$), and $p = h_e/h$. Within the range of aortic wall strain assessed, we assumed the stiffness of elastin to be constant and the stiffness of collagen to be incrementally recruited as modeled by Bank et al[21] (Figure 2). This assumes that E_c increases linearly with strain as previously reported[22]; thus, E_{inc} was evaluated as,

$$E_{inc} = pE_e + (1-p)E_c \frac{(\varnothing - \varnothing_0)}{\varnothing_0}. \tag{4}$$

In the LE model, E_{inc} is treated as constant and therefore independent of diameter (ie, $p=1$).

In Bramwell and Hill original development of the Moens-Korteweg equation, aPWV is derived in terms of the relationship between changes in blood volume per unit length and changes in arterial pressure.[23] This can be simply modified to relate changes in diameter to changes in arterial pressure,

$$aPWV = \sqrt{\frac{V}{\rho}\frac{d(TMP)}{dv}} = \sqrt{\frac{\varnothing}{2\rho}\frac{d(TMP)}{d\varnothing}}. \tag{5}$$

Expressions for $\varnothing$ and $d(TMP)/d\varnothing$ can be found by rearranging, and then differentiating Equation 2, with respect to $\varnothing$, respectively, using either the NLE or the LE models. Substituting these into Equation 5, aPWV for a composite NLE, (PWV_{NLE}), aorta model can be expressed as,

$$aPWV_{NLE} = \sqrt{\frac{\gamma h \left(4 \left(3E_e\varnothing_0 - 2E_c(\varnothing_0 - \gamma) + 2E_c\gamma\right)\right)}{15\varnothing_0^3\rho}}, \tag{6}$$

where,

$$\gamma = \frac{\varnothing_0 \left(32E_ch - 24E_eh + 15\sqrt{\dfrac{64h\left(3hE_e^2 + 5\varnothing_0 E_c(TMP)\right)}{75}}\right)}{32E_ch}.$$

Then using the LE model (E_{inc}=constant), aPWV, (PWV_{LE}), can be expressed as,

$$aPWV_{LE} = \sqrt{\frac{3(TMP)\varnothing_0 + 8E_{inc}h}{6\varnothing_0\rho}}. \tag{7}$$

To examine the potential influence of altered elasticity of elastin and collagen, the same geometric parameters (h, $\varnothing_0$) were applied to both LE and NLE; h=2.5 mm and $\varnothing_0$=15 mm. Young moduli were then selected to indicate flexible elastin (E_e = 0.1 MPa), a stiffer collagen (E_c = 1.5 Mpa) for the NLE model; and a moderately stiff network of extended collagen, residual elastin, and extracellular matrix (E = 0.475 MPa) for the LE model.

Results

Clinical Study

Resting aPWV (at a TMP equal to resting MAP) was greater in hypertensive compared with normotensive subjects (897±50 cm/s versus 784±43 cm/s; P<0.05). Examples of beat-to-beat variation of aPWV, MAP, ITP, and TMP during a Mueller maneuver of gradually increasing intensity for a typical normotensive and hypertensive subject are shown in Figure 3. Changes in MAP were small in comparison with those of ITP, and therefore, changes in TMP were determined mainly by changes in ITP. In normotensive subjects, as ITP decreased and thus TMP increased, aPWV increased (Figure 3, left). However, in hypertensive subjects, there was little change in PWV with TMP (Figure 3, right). The dependence of mean, age-adjusted, aPWV on TMP in the normotensive and hypertensive groups is shown in Figure 4. When measured at fixed TMP of 96 mm Hg, aPWV was equal in hypertensive and normotensive subjects. However, dependence of aPWV on TMP was significantly greater in normotensive compared with hypertensive subjects (9.6±1.6 cm/s per mm Hg and 3.8±0.7 cm/s per mm Hg in normotensive and hypertensive subjects, respectively; P<0.01), leading to an intersection of the aPWV versus TMP relationships for hypertensive and normotensive subjects. Thus, isobaric aPWV was higher, equal, or lower in hypertensive subjects compared with normotensive subjects, depending on the level of TMP at which it was assessed (Figure 4). There was a modest change in heart rate with modulated TMP (3.1±0.70 bpm per 10 mm Hg). However, the difference in dependence of PWV on TMP between hypertensive and control subjects
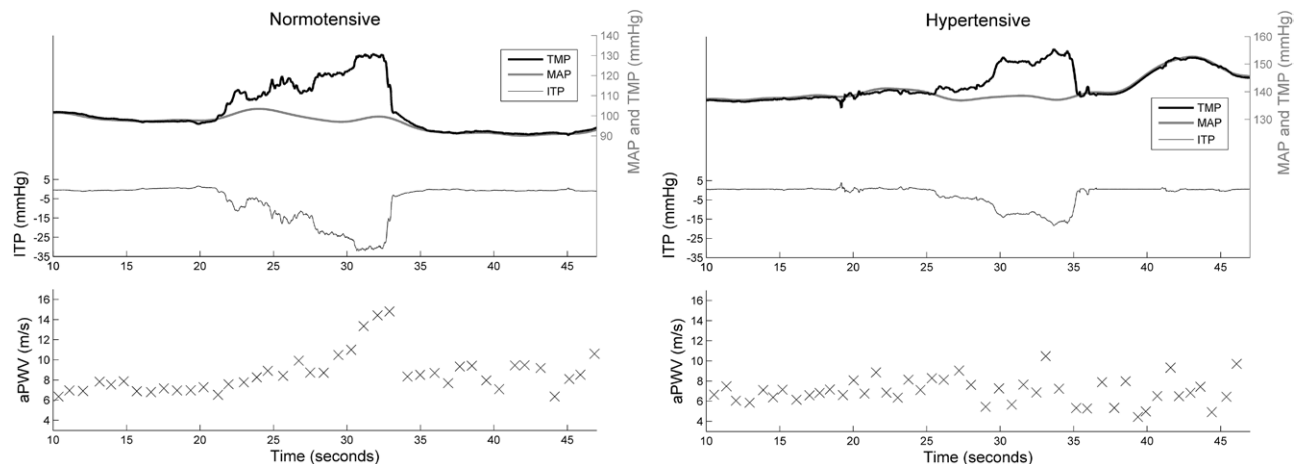
Figure 3. Examples of beat-to beat intrathoracic pressure (ITP), mean arterial pressure (MAP), aortic transmural pressure (TMP), and aortic pulse wave velocity (aPWV) measurements derived from Doppler ultrasound in normotensive (**left**) and hypertensive (**right**) subjects.

was similar, irrespective of whether results were or were not adjusted for heart rate.

Because the wide range of measured aPWV and resting blood pressures (and hence resting TMP) within both normotensive and hypertensive groups might reduce the dependence of aPWV on TMP, we examined variation from each individual's resting state, that is, the variation from resting aPWV and resting TMP (Figure 5). This revealed greater discrimination between hypertensive and normotensive groups in dependence of aPWV on TMP: dependence of aPWV on TMP in the hypertensive group (0.12±0.17% per mm Hg) was <20% of that in the normotensive group (1.16±0.14% per mm Hg; $P<0.01$).

Theoretical Model

Assuming a nonlinear composite stiffness aortic wall model, as described in Equation 6, variation in elastin stiffness (E_e) or collagen through thickness fraction does not allow for an intersection of aPWV versus TMP profiles, as observed in the clinical study. Instead, increasing the portion of collagen (p) or stiffness of the elastin (E_e) displaces the aPWV-TMP profile along the aPWV axis (Figure 6, top and middle). However, modeling the hypertensive case as a homogeneous linear structure, such as a network of extended collagen, residual elastin, and extracellular matrix, allows the intersection observed clinically to be reproduced (Figure 6, bottom).

Discussion

Whether hypertension is associated with an alteration in the intrinsic elasticity of the aorta or results in a stiffening of the aorta merely through a greater transmural stretching force is a fundamental question which has received surprisingly little attention. Previous studies to address this issue have examined the relationship of arterial pressure to diameter of the common carotid artery throughout the cardiac cycle with extrapolation to a common pressure. This approach suggests that, when compared at the same operating pressure, stiffness of the common carotid artery, as represented by Young elastic modulus (E) is similar in hypertensive and

in normotensive subjects.[7–9] However, the interpretation of such studies is limited by many factors. Comparison of distensibility at the same pressure relies on an overlap of arterial pressure in the 2 groups (ie, a measurement taken close to diastolic in the hypertensive group and close to systolic in the normotensive group). The interpretation of the result is, therefore, critically dependent on assumptions regarding the form of the pressure/diameter relation during the cardiac cycle and whether this differs in hypertensive and normotensive subjects. Calculation of E requires measurement of wall thickness, an assumption that the through-wall elasticity is constant and that intima-medial thickness (used to estimate the relevant wall thickness) is representative of the part of the wall that determines its overall elastic behavior. In reality, increased intima-medial thickness in hypertension may result from both intimal and medial thickening.[24] Finally, although carotid stiffness is closely correlated to aortic stiffness, it is of less prognostic impact than aPWV.[25]

Acute pharmacological manipulation of blood pressure using vasopressor and vasodepressor agents suggests a complex relation of aPWV with distending pressure which differs between normotensive and hypertensive subjects.[10] However,
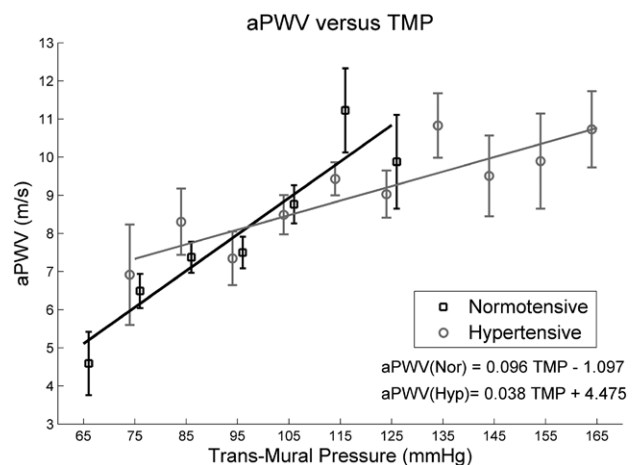
Figure 4. Dependence of aortic pulse wave velocity (aPWV) on transmural pressure in normotensive and hypertensive groups.
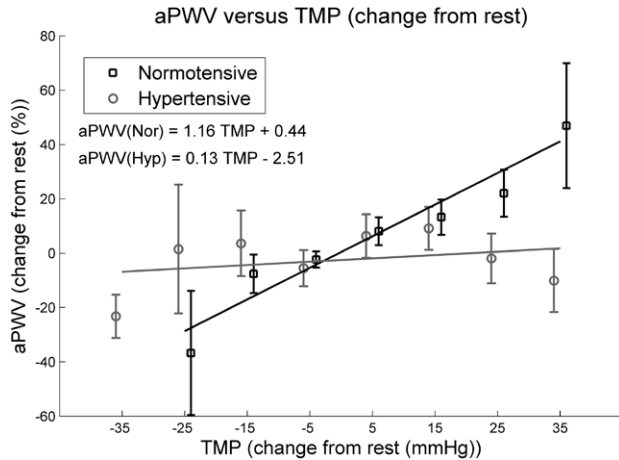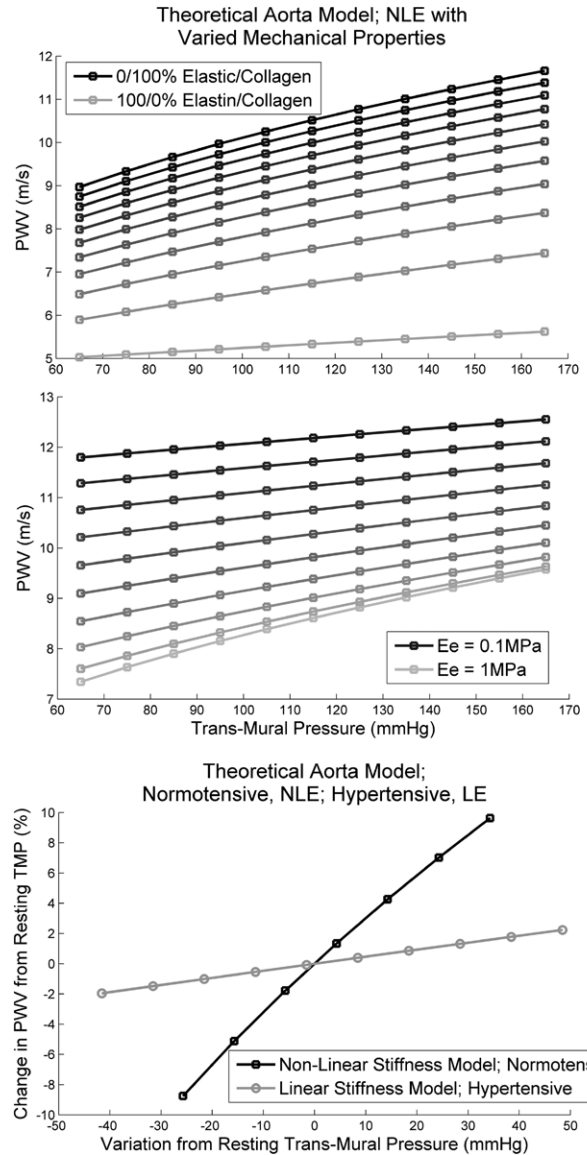
Figure 5. Change in aortic pulse wave velocity (aPWV) from resting values with change in transmural pressure (TMP) from rest in normotensive and hypertensive groups.

the interpretation of this work is limited by the range over which blood pressure can be modulated and possible effects of the drugs on arterial stiffness.

To our knowledge, this is the first study to have examined the relation between aPWV and TMP in vivo in man using a direct mechanical approach to modulate TMP, and the results reveal structural change in the properties of the aorta in hypertensive compared with normotensive subjects that cannot be appreciated from simple resting measures of aPWV. In normotensive subjects, the results demonstrate an increase in aPWV with increasing TMP, replicating results observed during mechanical manipulation of blood pressure in the canine aorta[6] and increase in blood pressure in humans achieved by infusion of angiotensin II.[10,26] By contrast, in hypertensive subjects, aPWV is seen to show little variation with TMP. Therefore, the higher potential for increased aortic wall stiffening with increased distending pressure in normotensive subjects, when compared with hypertensive subjects, means that a comparison of isobaric aPWV (ie, aPWV measured at a fixed TMP) will depend on the applied TMP. For example, if a TMP is applied, which is below the usual operating pressures in normotensive subjects, then a hypertensive subject is likely to have a higher isobaric aPWV compared with normotensive subjects, and at a TMP above the usual operating pressure in hypertensive subjects, the reverse is true. These results explain inconsistent findings with regard to isobaric stiffness in earlier studies.[7–10]

Increased aortic stiffening with increased TMP is usually attributed to progressive recruitment of collagen fibers, necessary to prevent overextension and rupture of the aortic wall. Our theoretical model of collagen recruitment (NLE model) reflects this increasing trend of wave speed, therefore stiffness, with TMP. Furthermore, the NLE model shows that as the proportion of collagen to elastin (p) or the Young modulus of elastin (E_e) increases, the aPWV versus TMP trend translates along the aPWV axis (a similar translation is also seen with variation of aortic wall thickness and diameter). The distinction we observed in hypertensive compared with normotensive

Figure 6. Theoretical variation in aortic pulse wave velocity (aPWV) vs transmural pressure (TMP) profiles in a nonlinear elastance (NLE) aorta model with varied elastin/collagen portions (top), and varied elastin stiffness, E_e (middle). Applying a composite NLE model as normotensive, and linear elastance model as hypertensive, an aPWV vs TMP intersection is theoretically possible. Model Parameters used were $\emptyset_0$=15 mm (unstretched), h=2.5 mm, P=0.6 elastin, and 0.4 collagen (measured in dogs).[26] In the NLE model, E_e=0.1 MPa and E_c=1.5 Mpa and in the LE model, E=0.475 MPa. See text for definition of parameters.

subjects did not display this upward trend but rather rotation of the trend, indicating that the composite stiffness model of elastin and fractionally recruited collagen may not accurately represent our hypertensive group. Instead, a linear stiffness hypertensive model (LE) offered a better reflection of our clinical observations, indicative of a group whose artery wall maintains a constant stiffness over the range of distension examined in this study. In this case, a network of extended collagen, residual elastin, and extracellular matrix would operate mechanically more like a stiff, homogeneous material.

Irrespective of the exact model invoked to explain the observed relation of aPWV with TMP, our results strongly suggest that hypertension is associated with a structural change in the aortic wall away from a composite NLE model leading to higher stiffness at normal operating pressures. Furthermore, there is a failure of stiffening to increase with increased TMP in hypertension, which may predispose to dissection of the wall when subject to a surge in pressure above the usual operating pressure.[27] Such a structural change could result from mechanical rupture of elastin and digestion of elastin through increased expression of matrix metalloproteinases.[28] However, we cannot exclude the possibility that the structural change precedes or indeed is causal to the development of hypertension.

Several important limitations of our study should be noted: the majority of our subjects had long-standing hypertension. It is likely that results may differ in subjects with new-onset hypertension. Most subjects were on treatment that might have influenced vascular smooth muscle tone in the aorta. However, previous studies have indicated that vascular smooth muscle tone in elastic arteries has little direct influence on thoracic aortic stiffness.[10,26] The respiratory maneuvers used to induce a controlled change in TMP are known to influence cardiac (contractility and stroke volume) and autonomic function over the course of the maneuver. Although theoretical considerations show aPWV to be independent of stroke volume,[23] it is possible that changes in cardiac function could have influenced aPWV. Against this is experimental evidence that aPWV is not influenced by inotropic stimulation with dobutamine (other than through an influence on MAP)[26] and the observation in the present study that aPWV tracked TMP throughout the respiratory maneuver (during which time cardiac output varies widely). aPWV is known to depend on heart rate.[29] However, the dependence is relatively weak and the size of the heart rate effect observed in previous studies would result in relatively minor confounding, which would be equal in normotensive and hypertensive subjects.

Perspectives

The present findings explain previous contradictory findings with respect to isobaric aPWV in hypertensive compared with normotensive subjects. Differing dependence of aPWV on TMP in normotensive and hypertensive subjects means that differences in isobaric aPWV depend on the TMP at which this is assessed. They suggest that hypertension is associated with a profound change in aortic wall mechanical properties with less strain-induced stiffening in hypertension compared with normotension that may reflect destruction of elastin and predisposition to aortic dissection.

In conclusion, we describe a novel method for examining the relation of aPWV to TMP based on modulation of ITP through respiratory muscle activity that provides measures of isobaric aPWV and pressure dependence of aPWV. The relation of aPWV to TMP differs in hypertensive and normotensive subjects, implicating a change in mechanical properties of the aorta in hypertension.

Disclosures

King's College London has formed a spin-out company to develop technology in central blood pressure measurement (not used in the present study). P. Chowienczyk has an interest in this company.

References

1. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55:1318–1327.
2. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107:139–146.
3. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension*. 2009;54:1328–1336.
4. McEniery CM, Spratt M, Munnery M, Yarnell J, Lowe GD, Rumley A, Gallacher J, Ben-Shlomo Y, Cockcroft JR, Wilkinson IB. An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly prospective study. *Hypertension*. 2010;56:36–43.
5. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation*. 1985;71:202–210.
6. Histand MB, Anliker M. Influence of flow and pressure on wave propagation in the canine aorta. *Circ Res*. 1973;32:524–529.
7. Laurent S, Caviezel B, Beck L, Girerd X, Billaud E, Boutouyrie P, Hoeks A, Safar M. Carotid artery distensibility and distending pressure in hypertensive humans. *Hypertension*. 1994;23(6 pt 2):878–883.
8. Armentano R, Megnien JL, Simon A, Bellenfant F, Barra J, Levenson J. Effects of hypertension on viscoelasticity of carotid and femoral arteries in humans. *Hypertension*. 1995;26:48–54.
9. Bussy C, Boutouyrie P, Lacolley P, Challande P, Laurent S. Intrinsic stiffness of the carotid arterial wall material in essential hypertensives. *Hypertension*. 2000;35:1049–1054.
10. Stewart AD, Jiang B, Millasseau SC, Ritter JM, Chowienczyk PJ. Acute reduction of blood pressure by nitroglycerin does not normalize large artery stiffness in essential hypertension. *Hypertension*. 2006;48:404–410.
11. Gosse P, Cremer A, Papaioannou G, Yeim S. Arterial stiffness from monitoring of timing of korotkoff sounds predicts the occurrence of cardiovascular events independently of left ventricular mass in hypertensive patients. *Hypertension*. 2013;62:161–167.
12. Gaddum NR, Schaeffter T, Bührer M, Rutten M, Smith L, Chowienczyk PJ, Beerbaum PB. Beat-to-beat variation in pulse wave velocity during breathing maneuvers. *Magn Reson Med*. 2014;72:202–210.
13. Scharf SM, Bianco JA, Tow DE, Brown R. The effects of large negative intrathoracic pressure on left ventricular function in patients with coronary artery disease. *Circulation*. 1981;63:871–875.
14. Imholz BP, van Montfrans GA, Settels JJ, van der Hoeven GM, Karemaker JM, Wieling W. Continuous non-invasive blood pressure monitoring: reliability of Finapres device during the Valsalva manoeuvre. *Cardiovasc Res*. 1988;22:390–397.
15. Virolainen J. Use of non-invasive finger blood pressure monitoring in the estimation of aortic pressure at rest and during the Mueller manoeuvre. *Clin Physiol*. 1992;12:619–628.
16. Evans DH, McDicken WN. *Doppler Ultrasound: Physics, Instrumental, and Clinical Applications*. Chichester, UK: John Wiley; 1999.
17. Gaddum NR, Alastruey J, Beerbaum P, Chowienczyk P, Schaeffter T. A technical assessment of pulse wave velocity algorithms applied to non-invasive arterial waveforms. *Ann Biomed Eng*. 2013;41:2617–2629.

18. Matthys KS, Alastruey J, Peiró J, Khir AW, Segers P, Verdonck PR, Parker KH, Sherwin SJ. Pulse wave propagation in a model human arterial network: assessment of 1-D numerical simulations against *in vitro* measurements. *J Biomech*. 2007;40:3476–3486.

19. Alastruey J, Nagel SR, Nier BA, Hunt AA, Weinberg PD, Peiró J. Modelling pulse wave propagation in the rabbit systemic circulation to assess the effects of altered nitric oxide synthesis. *J Biomech*. 2009;42:2116–2123.

20. Paul B. Prediction of elastic constants of multi-phase materials. *Trans AIME*. 1960;218:36–41.

21. Bank AJ, Wang H, Holte JE, Mullen K, Shammas R, Kubo SH. Contribution of collagen, elastin, and smooth muscle to *in vivo* human brachial artery wall stress and elastic modulus. *Circulation*. 1996;94:3263–3270.

22. Sokolis DP, Kefaloyannis EM, Kouloukoussa M, Marinos E, Boudoulas H, Karayannacos PE. A structural basis for the aortic stress-strain relation in uniaxial tension. *J Biomech*. 2006;39:1651–1662.

23. Bramwell JC, Hill AV. Velocity of transmission of the pulse and elasticity of arteries. *Lancet*. 1922;1:891–892.

24. Van Bortel LM. What does intima-media thickness tell us? *J Hypertens*. 2005;23:37–39.

25. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation*. 2006;113:657–663.

26. Stewart AD, Millasseau SC, Kearney MT, Ritter JM, Chowienczyk PJ. Effects of inhibition of basal nitric oxide synthesis on carotid-femoral pulse wave velocity and augmentation index in humans. *Hypertension*. 2003;42:915–918.

27. Groenink M, Langerak SE, Vanbavel E, van der Wall EE, Mulder BJ, van der Wal AC, Spaan JA. The influence of aging and aortic stiffness on permanent dilation and breaking stress of the thoracic descending aorta. *Cardiovasc Res*. 1999;43:471–480.

28. Irtyuga O, Pimenova N, Voronkina I, Uspensky V, Moguchaya E, Boyarinova M, Moiseeva O. Role of extracellular matrix proteins, matrix metalloproteinase activity and arterial stiffness in ascending aorta dilatation. *Eur Heart J*. 2013;34:861.

29. Millasseau SC, Stewart AD, Patel SJ, Redwood SR, Chowienczyk PJ. Evaluation of carotid-femoral pulse wave velocity: influence of timing algorithm and heart rate. *Hypertension*. 2005;45:222–226.

Novelty and Significance

What Is New?

- A novel method for examining the relation of aortic stiffness to transmural pressure providing measures of aortic pulse wave velocity (aPWV) at fixed pressure (isobaric aPWV) and pressure dependence of aPWV.
- Pressure dependence of aPWV differs in hypertensive and normotensive subjects explaining previous contradictory findings with regard to isobaric aPWV.

What Is Relevant?

- Hypertension is associated with less strain-induced stiffening compared with normotension that may reflect destruction of elastin and predisposition to aortic dissection.

Summary

Measurement of aPWV during modulation of intrathoracic pressure by varying respiratory muscle activity allows the relationship of aPWV to transmural pressure to be assessed. Differing dependence of aPWV on transmural pressure in hypertensive and normotensive subjects means that differences in isobaric aPWV between hypertensive and normotensive subjects depend on the transmural pressure at which this is assessed. They suggest that hypertension is associated with a profound change in aortic wall mechanical properties with less strain-induced stiffening in hypertension compared with normotension that may reflect destruction of elastin and predisposition to aortic dissection.