Arterial Blood Pressure and Stiffness in Hypertension
Is Arterial Structure Important?

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Increasingly, in recent years, the stiffness of large elastic arteries has been recognized as a major determinant of vascular function and cardiovascular risk. The distally propagating arterial pressure pulse is reflected at arterial branch points (sites of impedance mismatch), and the velocity and magnitude of these reflections is determined by arterial stiffness. Whereas peripheral vascular resistance largely determines diastolic BP, central systolic BP and pulse pressure are influenced by the augmentation of aortic pressure because of wave reflections, as well as by the character of ventricular ejection. Increased stiffness leads to greater pulsatile stress and strain and may influence endothelial shear stress, contributing to remodeling and structural abnormalities of the blood vessel wall and to atherogenesis. An increase in aortic stiffness also results in an increase in left ventricular afterload and, consequently, myocardial oxygen consumption and compromise of myocardial perfusion during diastole, particularly in the subendocardial region. That central arterial stiffness is clinically relevant is evident from the studies showing a positive predictive value of aortic stiffness for cardiovascular risk in hypertension, although the precise mechanism of this association remains unclear.

Arterial stiffness is largely determined by 2 influences: first, those related to the arteries themselves (wall structure and function and lumen size); and, second, the mean distending arterial BP. The main load-bearing components of the arterial wall are elastin fibers, stiffer collagen fibers, and vascular smooth muscle. Smooth muscle contraction results in increased arterial stiffness because of a decrease in lumen size and shifting of load onto stiffer collagen fibers. Increasing mean distending pressure causes a small increase in lumen size. However, transfer of stress from elastin to collagen fibers outweighs this effect, leading to an exponential increase in arterial stiffness with pressure. Given that arterial stiffness is increased in patients with essential hypertension and that arterial remodeling is a recognized feature of hypertension, an important question has been whether increased aortic stiffness is fully accounted for by the increase in mean distending pressure or whether there are intrinsic wall changes secondary to structural or functional effects. Indeed, this may be of importance in selecting treatment for individual patients.

To examine what effects the inherent properties of the vessel wall have on arterial stiffness, measures such as compliance, distensibility, pulse wave velocity (PWV), or elastic modulus must be compared under isobaric conditions. Previous work has either used pressure-compliance curves with interpolation of stiffness at a given blood pressure (BP) or has normalized transmural pressure by placing the arm in a pressurized air chamber. However, in this issue of Hypertension, Stewart et al describe a method for generating isobaric conditions using a pharmacological intervention that acutely normalized the loading pressure in hypertensive subjects, dispensing with some of the assumptions associated with other methods. Stewart et al studied 20 subjects with treated but inadequately controlled essential hypertension and 20 matched normotensive controls. Acutely reducing mean arterial pressure in the normotensive subjects, using glyceryl trinitrate (GTN), caused a corresponding reduction in arterial stiffness, as quantified by carotid-femoral PWV (PWVCF) and carotid distensibility. However, when mean pressure in the hypertensive patients was reduced to the baseline level of the normotensive individuals, there was no change in either PWVCF or arterial distensibility. Furthermore, using angiotensin II to increase the mean arterial pressure of normotensive subjects to the baseline level of the hypertensive individuals, arterial stiffness increased but still remained lower in the normotensive subjects. These findings suggest that the increase in aortic stiffness seen in hypertensive patients is because of an increase in intrinsic wall stiffness rather than simply elevated BP and may also imply a degree of resistance to changes of distending pressure. Importantly, this is in contrast to results from experiments using alternative techniques, which suggest that the increase in arterial stiffness in hypertensive individuals is largely because of the increase in mean pressure.

The 2 questions one must surely ask are, first, why do these findings seem to disagree with the findings of others using different methodology, and second, what relevance might these observations have from a clinical perspective?

Estimation of isobaric compliance from pressure-diameter curves requires important assumptions to be made, and it can be argued that the full pressure–diameter relationship should be considered rather than 1 value in the cardiac cycle. Because the vessel wall is viscoelastic, luminal diameter at a given pressure is affected by the nature of the preceding pressure curve. This results in the compliance–pressure relationship exhibiting hysteresis, which must either be “removed” or ignored to create a curve from which compliance...
can be calculated at any given BP. This curve-fitting procedure may result in a potentially large error in the estimate of compliance and, additionally, mask differences between 2 clearly distinct pressure–compliance loops. Furthermore, this approach disregards potential differences in the pressure–compliance loop that might exist at truly different distending mean pressures. Normalizing transmural pressure using mechanical means removes the potential inaccuracy introduced by such mathematical assumptions. However, it ignores systemic hemodynamic differences, such as wave reflections, that may exist. It can also only be used to examine conduit vessels and not large central arteries. The administration of a pharmacological agent (in this case GTN) is, of course, not without problems either. Small doses of GTN do not seem to change BP or PWV. It is possible, however, that the larger doses of GTN used in this study altered the intrinsic aortic wall stiffness independent of the reduction in mean BP. Furthermore, the aortic wall response to GTN may have differed between the hypertensive and normotensive groups. Alternatively, the duration of GTN administration may have been of sufficient duration to induce reflex neurohormonal changes that may exist. It can also only be used to examine conduit vessels and not large central arteries. The administration of a pharmacological agent (in this case GTN) is, of course, not without problems either. Small doses of GTN do not seem to change BP or PWV. It is possible, however, that the larger doses of GTN used in this study altered the intrinsic aortic wall stiffness independent of the reduction in mean BP. Furthermore, the aortic wall response to GTN may have differed between the hypertensive and normotensive groups. Alternatively, the duration of GTN administration may have been of sufficient duration to induce reflex neurohormonal responses to the hypotension induced and act in a counter-regulatory way to maintain a higher PWV in the hypertensive patients: pressure-diameter relationships are captured within the pressure excursions of a single cardiac cycle and have the potential advantage that they are not subject to such unknown hemodynamic changes. This was a relatively small study, and the findings would benefit from confirmation, including studies in previously untreated patients. In addition, there is a lack of data describing the changes in arterial stiffness in response to acute BP lowering with drugs other than GTN, and this is an important area for future work. Nonetheless, use of pharmacological intervention to achieve isobaric conditions would seem more clinically applicable than previous methodology, given that PWV can adversely affect central BP and cardiac function and is closely linked to cardiovascular risk.

Why are these findings potentially clinically relevant? Arterial stiffness is a risk factor for cardiovascular disease, independent of BP, and the study from Stewart et al suggests that simply lowering BP may not necessarily be sufficient to address this important risk factor. Indeed, other work has shown that antihypertensive treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium-channel blockers reduces arterial stiffness, whereas thiazide diuretics have less favorable effects, and β-blockers have little impact. The study by Stewart et al suggests that hypertensive remodeling is likely to be important, so any beneficial response is likely to take time to occur, either through direct effects on the arterial wall or because of reduced shear stress or pulsatile load. This would fit with recent work showing that larger doses of perindopril increase distensibility while having no additional effect on BP, consistent with a direct effect on intrinsic wall stiffness. Some newer agents targeting endothelial dysfunction or those directly affecting arterial structure, such as advanced glycation end-product crosslink breakers, may also offer promise in this area. Nevertheless, the failure of arterial stiffness to improve with thiazides, drugs with established morbidity and mortality advantages in hypertension, serves as a reminder that BP reduction per se remains of prime importance. More work is clearly indicated, using the powerful tools now available, to establish the mechanisms whereby chronic lowering of BP, using established and newer agents, reduces arterial stiffness and improves clinical outcome.

Disclosures
None.

References
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