Arterial Stiffness and Hypertension
Emerging Concepts

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Arterial stiffness is increasingly recognized as an important prognostic index and potential therapeutic target in patients with hypertension. It is closely linked to, but by no means synonymous with, raised blood pressure, and its physiopathology is still not fully understood. Aortic stiffness and arterial pulse wave reflections are key determinants of elevated central systolic pressure and are associated with adverse cardiovascular outcomes, independent of blood pressure. Indeed, the 2003 European Society of Hypertension guidelines on the management of hypertension acknowledge the potential role of arterial stiffness measurement in clinical management[1] and have prompted the publication of a consensus document on the measurement of central blood pressure and hemodynamics.[2] A detailed expert consensus document has also been published on the methodologic and clinical issues around arterial stiffness.[3] Broader implementation of these techniques into routine care seems inevitable. In this review, we have examined recent research in this field published in *Hypertension*, focusing on mechanistic work, methods for measuring stiffness, important clinical associations, and effects of treatment.

Mechanisms and Causes of Arterial Stiffness

Hypertension and arterial stiffness are closely associated with age.[4] Degeneration of compliant elastin fibers, and deposition of stiffer collagen, is considered a key cause of age-related arterial stiffening. Moreover, blood pressure plays a significant role in determining vessel wall structure, with remodeling occurring to compensate for changes in wall stress. One potential mechanism is through matrix metalloproteinases, which modulate extracellular matrix proteins. When angiotensin II is given to mice, matrix metalloproteinase 9 activity is induced, resulting in enhanced collagen degradation. This improves the intrinsic distensibility of elastic arteries and, thus, blunts any blood pressure rise.[5] Impairment of this compensatory mechanism may, therefore, contribute to increased stiffness. The organization of elastic fibers is also important. Inhibition of the vascular adhesion protein semicarbazide-sensitive amine oxidase in a rat model results in reduced elastin fiber cross-linking, leading to morphological changes. This, in turn, increases vascular fragility and arterial stiffness.[6] In humans, aortic calcification has also been shown to be positively associated with both aortic stiffness and isolated systolic hypertension.[7] Previous work has demonstrated that pharmacological agents targeted at vascular wall structure (eg, "AGE" breakers targeted at age-related advanced glycation end-product cross-links[8]) can improve arterial compliance. Understanding the mechanisms underlying aortic calcification and defining the roles of semicarbazide-sensitive amine oxidase, matrix metalloproteinases, and similar molecules in the pathogenesis of human hypertension may lead to other novel therapeutic approaches.

In addition to having structural determinants, arterial stiffness is influenced by vessel function, with the endothelium and, in particular, NO playing key roles. Aortic pulse wave velocity (PWV) is associated with endothelial dysfunction in patients with isolated systolic hypertension, a condition resulting from large artery stiffening.[9] Interestingly, however, although the endogenous NO synthase inhibitors asymmetric dimethylarginine and L-N^G-monomethyl arginine are associated with classic cardiovascular risk factors and independently predict subclinical atherosclerosis, they do not appear to be associated with arterial stiffening.[10] This finding is in contrast to the acute effects of exogenous NO synthase inhibition and highlights potential difficulties with some models of endothelial dysfunction. Sharman et al[11] demonstrated that, in contrast to the situation at rest, acute inhibition of NO during exercise has no effect on arterial wave reflections, arterial stiffness, or peripheral pressure amplification. Our understanding of dynamic changes in arterial stiffness remains poor and more work is needed, particularly given the benefits of exercise to cardiovascular health. However, whether these findings are attributable to an overwhelming effect of other vasoactive substances or simply a compensatory response to NO blockade remains uncertain. The effects of chronic changes in NO on exercise hemodynamics are also unknown, and the influence of improving NO bioavailability over a prolonged period on cardiovascular risk, atherosclerosis, or arterial stiffening should be a focus of future work.

Much research centers on the functional and structural aspects of the vessel wall but less on wall geometry. How-

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ever, changes in wall structure lead to changes in vessel diameter, with mechanical fatigue causing passive dilatation. There is increasing evidence that a small aortic diameter is linked to increased pulse pressure,[12] although this may only hold after adjustment for mean distending pressure.[13] A smaller aortic diameter might explain the more marked age-related increase in pulse pressure in women,[14] although it does not entirely account for sex differences.[15] This appears at odds with the usual hypothesis of cyclic stress causing aortic dilatation. One potential reason is that a smaller aortic cross-section results in greater impedance to pulsatile flow for a given wall stiffness and, consequently, an increase in pulse pressure. An attenuation of the usual age-related dilatation, perhaps attributable to some of the mechanisms influencing wall structure described above, may explain the elevation in systolic pressure. The possibility of using aortic dimensions as a useful means of predicting future development of systolic hypertension is interesting. Longitudinal studies are required to confirm causality, however, and additional questions remain regarding the time point during the cardiac cycle and the anatomic location at which aortic dimensions should be determined.

A number of studies have examined the role of inflammation in the development of arterial stiffness; indeed, a number of inflammatory biomarkers show weak associations.[16] The association of C-reactive protein (CRP) with wave reflections[16] is in contrast to other previous work.[17] More importantly, although CRP levels are positively correlated with aortic PWV in healthy men and CRP gene polymorphisms were associated with circulating CRP levels, the polymorphisms were not associated with aortic PWV.[18] This implies that CRP may simply act as a marker of vascular injury rather than being a direct contributory factor. Although this does not affect the prognostic value of CRP, and perhaps other such biomarkers, it does suggest caution in developing potential treatments targeted on this approach.

Female hormones may be another important factor influencing arterial wall behavior. In postmenopausal women, prolactin levels are positively associated with central systolic pressure, large artery stiffness, and cardiovascular risk.[19] Hormone replacement therapy is common in postmenopausal women, despite persistent doubts over its cardiovascular safety, the cause of which is uncertain. Langrish et al[20] demonstrated that standard hormone replacement therapy results in higher blood pressure than physiological levels of hormone replacement, yet no differences in arterial stiffness were observed. This could suggest that adverse effects of estrogen on blood pressure are counterbalanced by beneficial effects on intrinsic wall stiffness, perhaps through modulation of endothelial function. Arterial stiffness and augmentation index (AIx) also vary throughout the menstrual cycle and during pregnancy and are elevated in preeclampsia.[21] These findings emphasize the importance of taking the menstrual cycle into account when carrying out arterial stiffness studies in women and also raise the question of whether disturbances in arterial stiffness might precede the development of preeclampsia.

Methodologies

Of course, for useful research, arterial stiffness needs to be reliably quantified. Aortic PWV arguably remains the noninvasive gold standard. Applanation tonometry between carotid and femoral arteries is a particularly attractive means of determining aortic PWV, given its speed and simplicity. Indeed, transcutaneous measurements compare favorably with MRI-derived PWVs.[22] However, despite its reproducibility and strong association with clinically relevant outcomes, the technique is hindered by the intimate nature of femoral pulse acquisition. Alternative approaches are, therefore, of interest. Pulse wave analysis (PWA) uses peripheral arterial waveforms to provide estimates of central systolic pressure and AIx. This can be achieved either by using direct carotid artery measurements as a surrogate for the aorta or by applying a mathematical transfer function to radial artery measurements. PWA indices are associated with various cardiovascular outcomes, but, as evidenced by their independence from PWV, they cannot be considered direct indicators of stiffness. Various alternative approaches to PWA, and to assessing arterial stiffness in general, have been considered over the last couple of years.

The ambulatory arterial stiffness index (AASI) was described first by Li et al,[23] and uses the regression slope of the correlation between diastolic and systolic measurements during 24-hour ambulatory blood pressure recording. However, its use as a surrogate marker of arterial stiffness has been called into question.[24] Only a relatively weak correlation exists between AASI and aortic PWV, which fails to hold after adjustment for confounding variables.[24] AASI appears more strongly associated with the degree of diastolic pressure variability and the extent of nocturnal dipping.[24] Correcting for the strength of correlation of the AASI regression line appears to improve the association of AASI with other determinants of stiffness,[25] although whether this affects the relationship with direct measures of stiffness remains unanswered. Westerhof et al[26] have elegantly demonstrated using basic theoretical principles that AASI depends on both the heart and arterial system, and, therefore, despite correlating with arterial compliance, it should be considered a ventriculoarterial coupling factor. Regardless of the clinical significance of AASI, it cannot be used as an alternative to formal measures of stiffness.

PWA is widely used as a surrogate measure of stiffness and a method of quantifying wave reflections. Much of the work published in this field uses peripheral-to-central arterial pressure transfer functions, as implemented in the SphygmoCor system (AtCor Medical). The transfer function has been validated in several studies, although it does not remain without critics. One recent interesting observation is that the height of the peripheral pressure wave inflection corresponds reasonably to central systolic pressure, possibly obviating the need for a transfer function in the first place.[27] Assumptions about the constancy of this observation can obviously be subjected to the same criticisms as the transfer function, and the late systolic inflection may not always be easily identifiable. However, removal of the mysterious mathematical tool that is the transfer function may be more acceptable to sceptics. Of course, one further problem with PWA as a

measure of stiffness is that the wave shape is not only influenced by the velocity of reflected waves but by the magnitude of these reflections and the character of ventricular ejection. By simultaneously measuring flow, it is possible to decompose the arterial pressure wave into forward and backward components, providing an estimate of wave reflection not confounded by other factors. The use of a triangular estimate of flow also circumvents the need for additional arterial Doppler measurements, although the accuracy of this approach has been called into question, and more physiologically shaped estimates of flow have been proposed.[28] As well as providing an estimate of reflection magnitude,[28] these techniques have been used to estimate carotid-femoral transit time, albeit with only a modest correlation.[28,29] However, it has been shown that, because there is an uncertain time delay introduced at the reflection site, it is not possible to know the true pulse transit time; thus, the site of reflection (and, hence, wave velocity) cannot be accurately determined.[30] Nonetheless, estimation of reflection magnitude may still provide additional information to AIx alone, and it would be interesting to see whether this methodology has diagnostic or prognostic use.

Ultrasound measurements provide additional value over pressure measurement alone. Simultaneous recording of carotid diameter and pressure appropriately differentiates the effects on arterial elasticity of aging and blood pressure change.[31] Because it measures the wave contour rather than simply pressure extremes, it can also identify differences in stiffness between systole and diastole consistent with the viscoelastic nature of the vessel wall. Moreover, it permits assessment of short-term variability (ie, between individual cardiac cycles) in elasticity. Another interesting approach is the use of high-resolution, multiarray tracking to noninvasively assess bending strain in atherosclerotic plaque. This has been used to show that established risk factors, including hypertension, are associated with inward bending strain.[32] Most other approaches to evaluating arterial mechanics examine disease-free vessels. It remains to be seen whether these differences in stress are associated with increased risk of plaque rupture and subsequent adverse clinical events.

Clinical Associations

There are well-recognized associations between traditional cardiovascular risk factors and measures of arterial stiffness. The adverse consequences of such factors on stiffness appear to be reversible, as demonstrated in hypertensive smokers.[33] Conversely, rapid weight gain with visceral fat accumulation appears to be associated with the development of arterial stiffening, although this may in part be attributable to rises in blood pressure.[34] The finding that the normoglycemic healthy offspring of patients with type II diabetes mellitus have decreased arterial distensibility and greater pulse pressure also suggests that arterial stiffening may occur at an early stage,[35] despite apparently normal arterial structure. Indeed, obesity has been found to be associated with stiffening even in children.[36] Arterial stiffness appears to be affected by the presence of increasing numbers of components of the metabolic syndrome,[37] although the mechanisms remain unclear. Potential causes include inflammation, dyslipidemia, and oxidative stress, although these are rarely taken into account as independent confounding factors. It is also worthwhile remembering the confounding nature of blood pressure in such studies. For instance, obstructive sleep apnea has been found to be associated with decreased carotid distensibility, but only in the presence of hypertension,[38] although this study may be underpowered to show the association in those with normal blood pressure. However, isolated nocturnal hypertension is associated with increased arterial stiffness,[39] suggesting that increased functional stiffness attributed to greater mean distending pressure is not the sole explanation and that other structural vascular changes are occurring as a consequence of elevated pressure.

Numerous studies have now established aortic stiffness, usually measured by PWV, as an independent predictor of cardiovascular events. However, the use of PWA measures, including central pulse pressure, is less clear. Brachial pulse pressure is dependent on arterial stiffness and is well established to be associated with adverse cardiovascular outcome, although whether it is better than systolic and diastolic pressures alone remains contentious.[40] Because central pressure is a more important determinant than peripheral pressure of myocardial perfusion and cardiac work, its measurement may be preferred to traditional brachial values. Indeed, the Strong Heart Study demonstrated that central pulse pressure is more predictive of atheroma and adverse outcome than both peripheral pulse pressure and systolic pressure[41] in patients without overt cardiovascular disease. Similar findings have been obtained in patients undergoing nonemergency angiography for suspected coronary heart disease.[42] It is also possible that central pulsatility, calculated as pulse pressure divided by mean pressure, may have an even stronger association with adverse outcome.[42] Importantly, the discrepancies between central and peripheral pulse pressures do not appear to be entirely accounted for by traditional cardiovascular risk factors, highlighting the potential importance of measuring central pressure as an additional variable for risk stratification.[43] The substantial overlap between categories of peripheral blood pressure when considering the corresponding central pressure also has important implications for hypertension treatment.[43] Interestingly, lower diastolic pressure, itself dependent on greater arterial stiffness and pressure augmentation, is associated with increased mortality, independent of aortic PWV,[44] emphasizing the importance of wave reflections over and above aortic stiffness alone. There is also increasing evidence for an association between arterial stiffness and subclinical cerebrovascular disease. A cross-sectional study has shown an association between aortic PWV and silent cerebral small-vessel disease.[45] There are also data showing that increased stiffness is associated with,[46] and indeed predictive of,[47] cognitive decline in individuals without dementia. Although the mechanisms remain unclear, one might suspect a vascular etiology.

Therapeutic Options

Given the association between stiffness and cardiovascular outcome, the possibility of using stiffness as a treatment target is of major interest. Antihypertensive drugs generally result in a decrease in arterial stiffness, mediated through a

reduction in mean distending pressure. However, the fact that different antihypertensive agents may have different effects on outcome, despite similar blood pressure–lowering effects, raises the question of whether outcome differences can be explained on the basis of variations in effect on the intrinsic stiffness of the arterial wall.

A recent study compared for the first time the effects of the 4 main classes of antihypertensive agent on arterial stiffness and wave reflection in isolated systolic hypertension. Despite similar peripheral blood pressure lowering effects, only angiotensin-converting enzyme inhibition, calcium channel blockade, and diuretic therapy reduced central pressure, whereas β-blockade did not.[48] Significant reductions in AIx were observed with calcium channel blockade only, whereas β-blockade had the opposite effect. Furthermore, none of the 4 drug classes reduced aortic PWV. The latter may reflect the marked structural stiffening occurring with this condition, unresponsive to the relatively short (10-week) period of treatment. In hypertensive patients with type II diabetes mellitus, treatment with a combination of angiotensin receptor blocker and thiazide diuretic resulted in a greater improvement in arterial stiffness over a 6-month period than that seen with a calcium channel blocker,[49] despite similar hypotensive effects. No differences in AIx were observed. The authors assessed the effects on various measures of oxidative stress and endothelial function but only found a single measure of oxidative stress to differ between the 2 treatment groups, leaving the mechanism for the differences unexplained. In the Australian National Blood Pressure Trial, no differences in central blood pressure were observed between angiotensin-converting enzyme inhibitor and diuretic-based antihypertensive regimens, despite better clinical outcomes in the former treatment group.[50] However, direct measures of stiffness were not reported. This appears to be in contrast to the Conduit Artery Function Evaluation Study, although the differences in central pressure observed in the Conduit Artery Function Evaluation Study may have been accounted for by reductions in heart rate in the β-blocker group, compounded by the lack of pretreatment central pressure measurements.[51] In a further study, a median treatment of >4 years with angiotensin-converting enzyme inhibition resulted in no change in AIx compared with placebo, in spite of reductions in central PWV.[52] An attenuation of the initial reflex changes in heart rate or peripheral resistance, which may result in decreased pressure augmentation in short-term studies, has been proposed to account for these findings. From these relatively diverse observations, it is evident that the impact of drug therapy on the interplay between large artery stiffness and wave reflections has not been satisfactorily explained and emphasizes the importance of measuring both of these factors in clinical trials.

The drugs used in the studies described above are all well established in the management of hypertension, but it is worthwhile considering alternative approaches. A reduction in arterial stiffness has been described recently in patients with chronic kidney disease treated with acute endothelin-A receptor blockade.[53] These effects occurred on top of the usual renin-angiotensin system blockade and were not entirely accounted for by blood pressure lowering, having a more profound impact on stiffness than similar pressure reductions using nifedipine. The additional benefit of a reduction in proteinuria was observed. Patients with renal disease have considerably elevated cardiovascular risk, for which increased arterial stiffness is an independent prognostic marker. Furthermore, reductions in proteinuria reduce chronic kidney disease progression and subsequent adverse cardiovascular outcome. Additional studies of endothelin antagonism are warranted to evaluate the effects of prolonged treatment and to look for improvements in outcome not only in chronic kidney disease but also in other conditions associated with large artery stiffening. Disappointingly, there has been little development in the field of drugs targeted directly at the arterial wall structure, such as the promising work carried out with AGE breakers.[8] Given the continuing improvements in our understanding of the molecular structure of the vessel wall, this remains a key area of interest.

Perspectives

Our understanding of the mechanisms underlying arterial stiffness continues to grow rapidly, and inflammation, calcification, vascular growth and remodeling, and endothelial dysfunction may all be important. The ongoing development of methods for evaluating arterial stiffness in vivo will facilitate the translation of some of this clinical research into practical application. Indeed, clinical studies have already established that arterial stiffness is independently associated with cardiovascular outcome in most of the situations where it has been examined. Furthermore, a number of therapies can reduce arterial stiffness. We have yet to show, however, whether agents that reduce arterial stiffness also reduce cardiovascular events independent of any of their other effects on recognized risk factors, such as blood pressure. This is the critical next step for arterial stiffness research.

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