Arterial Stiffening
Cause and Prevention

Marina Cecelja, Philip Chowienczyk

Aort and large artery stiffening, hallmarks of vascular aging, are predictive of cardiovascular events, particularly in subjects with hypertension and components of the metabolic syndrome. One hypothesis is that stiffening is a consequence of the combined insult of risk factors on the vascular wall. However, cross-sectional studies show little association of arterial stiffness with conventional risk factors other than blood pressure. The interrelationship of arterial stiffness with blood pressure makes it fascinating for the hypertensionologist. An elevation in mean arterial pressure stretches the arterial wall, leading to a functional increase in stiffness. Stiffening associated with a chronic elevation of blood pressure (ie, hypertension) may be because of distention of the arterial wall but could also be explained by structural changes of the arterial wall. The degree to which the latter explains hypertension-associated stiffening is still disputed. Finally, the effect of increased stiffening is to increase pulse pressure and systolic blood pressure. Disentangling these interrelationships is challenging, and the causal link between blood pressure and arterial stiffness has not been elucidated. Longitudinal studies that provide insight into the role of blood pressure and novel risk factors on arterial stiffening are, thus, particularly useful.

In this issue of Hypertension, McEniery et al present an analysis of prospective risk factors for aortic stiffness in men from the Caerphilly Prospective Study. In a cohort of 825 men of mean age 74 years, aortic pulse wave velocity (PWV), regarded by many as the gold-standard measure of arterial stiffness, was measured during the most recent follow-up phase of the Caerphilly Prospective Study. The relationship of PWV to blood pressure and risk factors at the time of its measurement and over an average follow-up of 20 years was examined. PWV (adjusted for “current risk factors”) was closely correlated with the pulse pressure×heart rate product over the 20-year follow-up. There was also a highly significant correlation of PWV with baseline and subsequent measures of C-reactive protein. Aside from weak correlations with blood glucose, triglycerides, and waist diameter, PWV was not correlated with any other risk factor. A limitation of the study, which the authors were keen to point out, is that they did not have longitudinal measures of PWV. Thus the association of PWV with longitudinal measures of pulse pressure could be explained by pulse pressure acting as a surrogate for PWV. Similarly, the contribution of heart rate could be explained in part by the functional increase in PWV that accompanies an acute elevation in heart rate and that is probably attributable to visco-elastic properties of the arterial wall. Nonetheless, the finding of a relationship between PWV and repetitive cyclic stress is appealing, because such stress is thought to result in stress fracturing of elastin and consequent stiffening.

How does the other major finding of this study, the association of PWV with CRP, fit with our understanding of the pathophysiology of arterial stiffening? CRP is a recognized biomarker of atherosclerosis. Could atherosclerosis cause arterial stiffening? Lack of association of PWV with conventional risk factors for atherosclerosis in this and other studies makes this seem unlikely. Furthermore, in animal studies, atherosclerosis, at least in its early stages, is not associated with increased stiffness. An alternative possibility is that inflammation is directly or indirectly related to increased aortic stiffness through mechanisms that are, at least in part, distinct from atherosclerosis. Vascular calcification is a process thought to be driven by inflammation. Animal models of arterial calcification result in a marked increase in stiffening and calcification is thought to cause arterial stiffening in chronic kidney disease, and McEniery et al have previously demonstrated a relation between arterial calcification and stiffening in the general population. A distinction is often made between diffuse medial calcification occurring in diabetes mellitus and chronic kidney disease and focal calcification localized to atherosclerotic plaque, but these 2 conditions may represent extremes of a continuum. A hypothesis that links the present findings in the Caerphilly Prospective Study and previous studies is that mechanical stress and/or genetic variants in elastin structure result in stress rupturing of elastin, which acts as a focus for calcification, a process accelerated by the presence of inflammation and chronic kidney disease (Figure). Elegant imaging studies in mouse models demonstrate microcalcification of elastin-rich structures, such as the aorta occurring in parallel with inflammatory activity. In humans, hybrid fluorodeoxyglucose-positron emission tomography/computed tomography imaging demonstrates stiffness to be associated with both calcification and inflammation. Imaging modalities, such as computed tomography, do not reveal microcalcification, but it is likely that this is associated with the macrocalcification seen in subjects with increased arterial stiffness (Figure). It is less certain whether systemic inflammation arising from a stimulus other than atherosclerosis.
promotes calcification. However, medial calcification is thought to be associated with inflammation, and it is notable that chronic inflammatory conditions, such as rheumatoid arthritis, are associated with increased arterial stiffness.10 These ideas need testing by investigating effects of interventions on this pathway to prevent arterial stiffening. Low-ering blood pressure, particularly pulse pressure, is an obvious intervention. Reducing heart rate with β-blockers introduces the complication that aortic-brachial pressure amplification is increased, but if antihypertensive therapy were titrated to central blood pressure, β-blockade might be effective. There is emerging evidence that anti-inflammatory therapy may reduce arterial stiffness.10 Finally, if calcification does prove to be causally related to stiffening, understanding the biology of vascular calcification may reveal a number of targets to prevent stiffening. It is intriguing, for example, that, in animal models, bisphosphonates reduce arterial calcification.11 Such an effect might contribute to the improvement in survival associated with bisphosphonate use. A challenge for such trials is that they will need to be powered to detect a reduction in the rate of progression of arterial stiffening and, thus, will require relatively long follow-up.

Sources of Funding
We acknowledge support from the British Heart Foundation and from the Department of Health via the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy’s and St. Thomas’ National Health Service Foundation Trust, in partnership with King’s College London and King’s College Hospital National Health Service Foundation Trust.

Disclosures
None.

References