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Arteriosclerosis and Atherosclerosis Guilty by Association

Ian B. Wilkinson, Carmel M. McEniery, John R. Cockcroft

Over the last decade, there has been a dramatic resurgence of interest in large-artery hemodynamics. This has been driven principally by the accumulating evidence that aortic stiffness is an independent predictor of future cardiovascular risk in a variety of populations.¹ The current gold-standard measure of aortic stiffness is aortic pulse wave velocity (aPWV). This reflects the fact that it has the most evidence relating to outcome and that it can be reliably assessed between the carotid and femoral arteries, noninvasively.¹ However, there continues to be considerable debate about the nature of the relationship between arterial stiffness and cardiovascular disease: is aPWV truly an independent risk factor or simply a marker? A number of hypothetical relationships exist (Figure), as described below.

First, aortic stiffening may promote cardiovascular disease independent of other more established cardiovascular risk factors. Data from some of the published outcome studies would support this view, but it is likely that meta-analysis of these data will be required to demonstrate this convincingly.

Second, an alternative suggestion is that aPWV simply represents the integrated effects over time that established risk factors have on the arterial wall and that stiffening of the wall does not in itself cause disease. Nevertheless, aPWV could still be more closely related to future events than a single “snapshot” measure of individual risk factors in isolation. A simple analogy is weight, which represents the integrated relationship between food intake and energy expenditure over an individual’s lifetime and, thus, is a more reliable measure of overall energy balance than a single day’s assessment of energy intake and usage.

Third, if the presence of atheroma alters the mechanical properties of the arterial wall, then aPWV could simply be a measure of the amount of plaque between the carotid and femoral arteries.

Dissecting out the precise relationship between arterial stiffness, established cardiovascular risk factors, and cardiovascular disease, and, ultimately attributing causality, requires large-scale, prospective studies, with repeated measurements of risk factors, aPWV, and cardiovascular events.

Such data do not currently exist, but a variety of cross-sectional observations are available. Unfortunately, the results are conflicting, no doubt reflecting small samples sizes and incomplete data sets but also differing statistical methodologies. For example, not all investigators routinely adjust for age and mean arterial pressure or other risk factors. This seriously limits our ability to interpret their findings, not only because of the natural tendency for cardiovascular risk factors to cluster together but also because stiffness depends on the pressure (mean arterial pressure) at which it is measured. Moreover, investigators sometimes use arbitrary cutoffs or analyze their data by “number of risk factors” rather than treating the data as the continuous variables that they are. Not only does this go against the wealth of epidemiological data indicating that risk factors tend to be continuously related to outcome measures, but it substantially reduces the power of the study.

It is against this backdrop that Cecelja and Chowienczyk² present the results of a systematic review of the literature concerning aPWV and cardiovascular risk factors. They identified 76 studies containing data relating aPWV to age, blood pressure, and a variable number of other cardiovascular risk factors, in which regression models were available. Their headline conclusion is that only age and blood pressure are consistently related to aPWV and that these 2 parameters explain the majority of the observed variability in the regression models. Not only were other risk factors much more weakly correlated with aPWV, but in the majority of studies they were no longer significant after adjusting for age and blood pressure, suggesting that they are relatively unimportant drivers of arterial stiffening compared with age and pressure. Interestingly, a closer look at the largest studies included in the review substantiates this view.

Although Cecelja and Chowienczyk² did not examine the relationship between atherosclerosis and aPWV, postmortem analysis of a large number of aortas from a Japanese cohort with antemortem aPWV measurements found only found a weak correlation between plaque load and aPWV.³ Moreover, careful analysis of the available cross-sectional observations concerning aPWV and coronary atherosclerosis reveals a similarly weak correlation with coronary plaque burden.⁴ Thus, aPWV is probably not a reliable measure of the extent of atherosclerosis or the effect that established risk factors have on the large arteries. This reinforces Pickering’s^{4a} view that atherosclerosis and arteriosclerosis (age-related stiffening and dilatation of the large arteries) are pathologically distinct and should be considered as separate disease processes.

So where does this leave the quest to understand the mechanism of arterial stiffening? Without question, age and blood pressure are very important determinants of aortic

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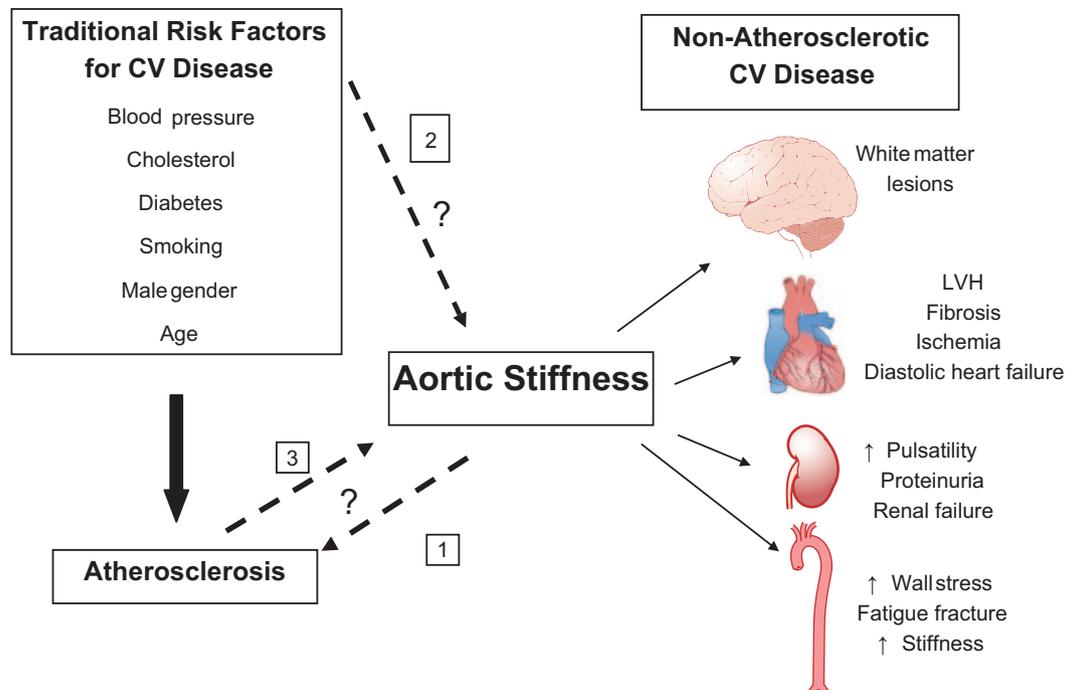


Figure. Proposed mechanisms linking aortic stiffness with atherosclerotic and nonatherosclerotic cardiovascular disease. Arrows numbered 1 to 3 refer to hypothetical relationships discussed in the text (first, second, and third).

stiffening. Other “traditional” cardiovascular risk factors seem much less important, but only longitudinal observations made over a prolonged period can exclude small but significant effects. We would strongly suggest that such studies are started in youth to minimize the initial confounding effects of atherosclerosis and pharmacological treatment. While we are waiting for these data, one potential way forward is a meta-analysis and metaregression of existing well-characterized cohorts with good phenotypic data.

The regression models from the largest studies reviewed by Cecelja and Chowienczyk² indicate that age and blood pressure account for $\approx 50\%$ of the variability in aPWV. Therefore, there are likely to be other risk factors for arteriosclerosis. Cross-sectional studies have identified potential candidates, including medial calcification,⁵ inflammation,⁶ and deposition of advanced glycation end products.⁷ The limited longitudinal data that are currently available indicate that adiposity and renal function may also be causally linked to aortic stiffening.^{8,9} However, it is likely that arteriosclerosis is the product of a complicated pathological process involving multiple pathways and triggers. Finally, the studies reviewed by Cecelja and Chowienczyk² assessed carotid femoral pulse wave velocity, and recent studies using MRI have demonstrated clear evidence of differential regional aortic stiffening, particularly between the ascending and descending aorta, and also that such differences in pulse wave velocity may be influenced by different factors. Therefore, the current review cannot rule out an effect of risk factors other than age and blood pressure on regional aortic stiffening. Such additional studies are needed, because they may lead to a more focused understanding of the mechanisms involved in arterial stiffening.

Clearly, genetic variation in the elastic components of the aorta is probably important. Twin studies give a heritability for aPWV of $\approx 40\%$, and several different approaches, such as the phenotyping of monogenic disorders, microarray analysis, and classic genetic association studies, have generated a list of plausible candidates, including elastin,¹⁰ matrix metalloproteinase 9,¹¹ and cell signaling molecules.¹² Large-scale, genome-wide association studies are likely to reveal more candidate genes, and the technique of mendelian randomization may prove useful in assessing their potential role in arteriosclerosis. However, the contribution of individual genes is likely to be small, and it would be foolish to believe that there are only a handful of genes, each with large effects. Perhaps a more fruitful use of genetic data will be the identification of novel pathways and targets for pharmacological intervention. Currently no drugs work directly to reduce aortic stiffness, and new therapies have the potential to reduce the burden of cardiovascular disease, especially in older subjects, or even to prevent/retard the process of arteriosclerosis itself.

A variety of mechanisms may be responsible for the association between age and aortic stiffening. Clearly, age is a measure of exposure to potential novel risk factors for stiffening; however, it is also a rough surrogate for the number of heartbeats an individual has experienced since birth. Theoretical and animal data indicate that the rate of elastin fatigue fracture depends on the number of stress cycles and level of stress,¹³ that is, the number of heartbeats experienced and pulse pressure. This would explain why age and blood pressure are major determinants of aPWV and also offers an explanation for the cross-sectional relationship between resting heart rate and aPWV.^{14,15} However, this remains to be tested directly with longitudinal data from

cohorts with repeated measures of heart rate and blood pressure. Nevertheless, age-related arterial stiffening should not be viewed as inevitable. Data published >20 years ago demonstrate that there is much less age-related arterial stiffening in rural populations.¹⁶ No doubt, some of this difference may relate to a lower initial blood pressure in the rural setting, but other factors are likely to be important. This important observation implies that we may be able to delay arterial stiffening by intervening in susceptible groups. Certainly, in experimental animals, inhibition of the renin-angiotensin system attenuates arterial ageing.

Arteriosclerosis could directly promote cardiovascular disease in a number of ways. Stiffening of the large elastic arteries has a number of potentially detrimental hemodynamic consequences, including a rise in pulse pressure and a reduction in shear stress oscillations (rate). A low diastolic and high systolic pressure reduces myocardial blood flow while increasing left ventricular workload. This may ultimately lead to myocardial ischemia, fibrosis, and heart failure. A high pulse pressure may increase pulsatility in fragile capillaries, leading to damage, especially in high-flow, low-resistance organs, such as the kidneys and brain, and also accelerate aortic stiffening via increased wall stress. Such effects would mainly lead to nonatherosclerotic cardiovascular disease. However, low shear stress rate reduces endothelial NO production, accelerating atheroma formation.

Research into large arteries is now firmly out of the shadows and into the limelight. The time is now right to move away from simple cross-sectional observations and to start collecting prospective data, as well as to investigate the process of arteriosclerosis, which affects almost everyone and is likely to become one of the most important driving forces for cardiovascular disease in the new millennium.

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Disclosures

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