Aortic stiffness has re-emerged over the past 20 years as an important predictor of cardiovascular outcome. Despite this, we still know relatively little about the pathophysiological processes underlying large artery stiffening (ie, arteriosclerosis). In previous editorials, we emphasized that arteriosclerosis is a distinct pathophysiological entity, separate from atherosclerosis, and should not be considered as an inevitable part of aging. Although potential risk factors for arteriosclerosis have been identified from cross-sectional observations, there is a general lack of consistency between studies. This no doubt reflects methodological differences, often small sample sizes, bias, (un)known confounders (variably adjusted for), and reverse causality. Longitudinal observations deal with some of these limitations and, therefore, provide a better framework for investigating the drivers of arteriosclerosis and identifying potential stiffening risk factors.

For the past 10 years, very few longitudinal studies, with repeated measurement of aortic pulse wave velocity (aPWV), the currently accepted gold standard clinical measure of aortic stiffness, have been published. They range in size from 112 to 1759 subjects, with 2 to 7 years of follow-up. Therefore, it is particularly pleasing to see new data from the Baltimore Longitudinal Study of Ageing (BLSA). Although not particularly large, the BLSA has the added advantage of repeated observations. The data on diabetes mellitus are less clear-cut, and interpretation is complicated by the use of a variety of biomarkers, such as glucose, but rarely HbA1c, self-reporting, and blood pressure and heart rate only explain some of this variability. The popular view is that cardiovascular risk factors, other than systolic pressure and heart rate, are, if anything, higher in older women, as is the prevalence of isolated systolic hypertension. Interestingly, in the BLSA, male sex and obesity were associated with accelerated arteriosclerosis. The sex-effect is surprising not least because large-scale, cross-sectional observations report little difference in aPWV between sexes, as do other longitudinal studies. Moreover, pulse and systolic pressure are, if anything, higher in older women, as is the prevalence of isolated systolic hypertension.

Existing cross-sectional and longitudinal data on obesity and arteriosclerosis are contradictory. In the BLSA, waist circumference was related to accelerated stiffening in women but not in men. Part of the problem when investigating the role of obesity is the confounding effect of body habitus if surface distance is used to calculate aPWV—protruding abdomens increase the measured distance, artifically raising aPWV. The BLSA used a height-based distance to try to overcome this, which, as expected, attenuated the impact of waist circumference but did not remove its influence completely. These observations deserve further attention, as do the potential underlying mechanisms, especially as human aortic stiffness is largely structurally determined and, therefore, endothelial dysfunction seems an unlikely mediator.
Aortic stiffening has important clinical consequences, including systolic hypertension and increased cardiovascular risk. Although inevitable, for most of us, the precise mechanisms driving arteriosclerosis remain incompletely understood, minimizing therapeutic opportunities. Apart from blood pressure, other cardiovascular risk factors play little role in aortic stiffening, suggesting that there are as yet undiscovered mechanisms. Although several have been proposed, including inflammation and calcification, longitudinal data are generally lacking. Future studies investigating potential biomarkers in arteriosclerosis will need to be large, with long follow-up, and careful, repeated measurements of aortic stiffness. An ongoing meta-analysis of the existing longitudinal data may also prove to be a useful interim step but may have limited ability to assess novel biomarkers.

Disclosures
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References

Figure. The vicious circle of arteriosclerosis. Fatigue-fracture of the elastic elements in the aorta leads to elevated systolic pressure and thus increased cyclic stress—setting up a vicious circle. Factors driving blood pressure elevation lead to increased systolic pressure, thereby accelerating the process, as do the factors driving arteriosclerosis. Ultimately, elevated systolic pressure and increased stiffness both lead to cardiovascular disease.
The Pressures of Aging
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