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 measures of aPWV for a 9-year average follow-up period, in men and women, and across a wide age range. The headline findings are that initial systolic pressure and age are the main drivers of arterial stiffening, that older men compared with women have a steeper rise in aPWV, and that traditional cardiovascular risk factors, other than systolic pressure and pulse pressure, have little impact on arteriosclerosis.

Increasing aortic stiffness acutely results in a rise in pulse and systolic pressures, leading some to view systolic hypertension as a consequence of aortic stiffening. Indeed, aPWV is increased in subjects with systolic hypertension, even after adjusting for differences in mean arterial pressure; and in the BLSA and Framingham Heart Study, aPWV predicts the change in systolic pressure with aging and development of hypertension. However, others think that elevated systolic (and pulse) pressure promotes degeneration of the arterial wall and thus aortic stiffening, as seen in these recent data from the BLSA. Other longitudinal studies are unhelpful in this respect, with 2 reporting that baseline systolic pressure is positively associated with aortic stiffening and 2 finding no such association. However, these hypotheses should not be viewed as mutually exclusive. More likely is that each begets the other (ie, higher systolic and pulse pressure early in life accelerate fatigue-fracture of the aortic elastic elements, resulting in wall stiffening, a loss of buffering capacity, and a further rise in pressure—setting up a vicious circle; Figure).

The positive association between baseline heart rate and aortic stiffening, in BLSA, would also fit with this model. Heart rate represents the frequency of aortic cyclic stresses, and, thus, when multiplied by age is a surrogate for the cumulative number of stress cycles. In the Caerphilly Heart Study, we found that aPWV was dependent on the product of pulse pressure and heart rate integrated >20 years.

Fatigue-fracture alone cannot be the single driver of aortic stiffening, not least because stiffening is highly variable, and blood pressure and heart rate only explain some of this variability. The popular view is that cardiovascular risk factors, such as cigarette smoking, also drive aortic stiffening. However, BLSA data suggest that they have little impact on aortic stiffening, substantiating previous longitudinal 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 a lack of distinction between types.

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
I.B. Wilkinson is a British Heart Foundation Senior Clinical fellow (WE Parkes). I.B. Wilkinson and C.M. McEniery are supported by the National Institute for Health Research Cambridge Biomedical Research Center.

References
The Pressures of Aging
Carmel M. McEniery and Ian B. Wilkinson

Hypertension. 2013;62:823-824; originally published online September 3, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.01998

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/62/5/823

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/