Large artery stiffness is an important mediator of cardiovascular disease. Aortic stiffening causally contributes to isolated systolic hypertension and increases left ventricular pulsatile hydraulic load, which is important in conditions such as heart failure, hypertensive heart disease, and valvular heart disease (particularly aortic stenosis). In addition, there is increasing recognition of the role of arterial stiffness on microvascular disease, which is relevant for the damage of target organs such as the brain and the kidney.

Consistent with the important role of arterial stiffness in cardiovascular health, measures of large artery stiffness have been shown to independently predict the risk of incident cardiovascular events in both clinical and community-based cohorts. However, the degree to which the relationship between large artery stiffness and incident cardiovascular disease is mediated by microvascular dysfunction is unclear. In this issue of Circulation: Cardiovascular Imaging, Cooper et al report the results of a large prospective cohort study that advances our understanding of this issue. The authors measured carotid–femoral pulse wave velocity (a measure of large artery stiffness) and brachial artery hyperemic mean Doppler flow velocity after an ischemic forearm occlusion (an index of microvascular function), among 4547 Framingham Heart Study participants. They performed analyses to relate individual measures of vascular function to incident cardiovascular disease, and subsequent mediation analyses to assess the degree to which prevalent microvascular dysfunction at baseline accounts for the prediction of cardiovascular events provided by carotid–femoral pulse wave velocity. Their results demonstrate that both higher carotid–femoral pulse wave velocity and lower hyperemic mean flow velocity were independently associated with incident cardiovascular disease. In mediation analyses, 8% to 13% of the relationship between aortic stiffness and cardiovascular events was explained by hyperemic mean flow velocity. The authors conclude that associations between aortic stiffness and cardiovascular events are mediated by pathways that include microvascular damage and remodeling.

To better understand the hemodynamic basis of the role of large artery stiffness on small vessel disease and to place the findings of Cooper et al in perspective, it is useful to consider the hemodynamic consequences of aortic stiffening on microvascular pressure and flow. Conduit arteries normally exert a powerful cushioning function, which delivers nearly steady flow in the microvasculature despite the intermittent left ventricular ejection. However, when the aortic wall stiffens as a consequence of aging and various pathological states (such as hypertension, diabetes mellitus, inflammation, chronic kidney disease, and yet unknown exposures), the cushioning function of the aorta is impaired. Aortic stiffening, therefore, promotes increased pulsatility in the microvasculature, particularly in organs that require torrential blood flow, and must operate at low levels of local microvascular resistance. Systemic organs that exhibit such richly perfused low-resistance vascular beds include the brain, the kidney, and the myocardium. Myocardial vessels demonstrate unique pulsatile pressure and flow characteristics because of the myocardial contraction, which compresses intramyocardial blood vessels, limiting systolic blood flow. In contrast, the microvascular beds of the brain and the kidney are exposed to upstream fluctuations of pressure and flow during both systole and diastole. In these organs, the effects of systemic large artery stiffening and the associated pulsatile hemodynamic abnormalities have important consequences for the microvasculature. Both increased pulsatile pressure (barotrauma) and pulsatile flow (with excessive pulsatile shear forces from increased pulsatile flow velocity) can result in microvascular damage in these organs. Consistent with these principles, accumulating evidence links cerebral microvascular disease and renal disease with increased aortic stiffness.

The effects of wave travel and reflection are of particular relevance for our understanding of microvascular damage associated with aortic stiffening. Every beat, the left ventricle generates a pulse wave that travels forward in the arteries and gets partially reflected at sites of impedance mismatch, such as points of branching or changes in vessel diameter or wall material properties along the arterial tree. Innumerable tiny reflections merge into a functionally discrete reflected wave, which travels back to the heart. In middle-aged and older adults, this reflected wave arrives at the aorta during systole, with important adverse consequences for central pulsatile hemodynamics. As mentioned by Cooper et al, aging is also associated with a disproportionate increase in aortic stiffness relative to muscular arterial stiffness, promoting impedance matching and a reduction in wave reflection in first-order
arterial bifurcations in older adults.\textsuperscript{12} Loss of wave reflection proximal to target organs (such as at the aorta–carotid interface) has been proposed as a mechanism underlying cerebrovascular damage from aortic stiffening. However, it should be noted that impedance matching is not only dependent on wall stiffness but also strongly dependent on vessel size.\textsuperscript{15} Therefore, despite substantial differences in pulse wave velocity between the aorta and muscular arteries, optimization of the size ratio between parent and daughter vessels in the arterial tree can greatly reduce impedance mismatch (relative to pulse wave velocity mismatch) even before the aorta stiffens with age. The configuration of parent and daughter arterial branches, which generally favors forward energy transmission, is also responsible for the fact that reflections at single bifurcations tend to be small, relative to the composite reflected wave arising from the sum of innumerable tiny reflections elsewhere. The bulk of wave reflections, therefore, arises from locations other than the first-order bifurcations leading to target organs (such as the brain), and in fact, the large reflected wave returning from the lower body penetrates the carotid artery as a forward wave (thus increasing pressure and flow in the carotid bed).\textsuperscript{3,16} Paradoxically, impedance matching between the aorta and the carotid artery also promotes the penetration of the reflected wave returning from the lower body into the carotid territory. Finally, arteries upstream of the cerebral microvasculature seem to be more effective at attenuating high-frequency flow pulsations (such as those contained in the early systolic carotid pulse peak produced by the initial cardiac contraction) than at attenuating low-frequency oscillations (which are preferentially contained in the reflected wave from the lower body).\textsuperscript{3,16} Clearly, it is not possible to generalize wave reflections as protective of target organs. Rather, the available elegant studies analyzing reflection phenomena at discrete interfaces\textsuperscript{12} are best interpreted in the context of the complexity of systemic arterial hemodynamics. These considerations have important therapeutic implications because systemic wave reflections are susceptible to modification by pharmacological interventions, which may influence our approach to the prevention and treatment of microvascular disease related to pulsatile arterial hemodynamics. In this regard, it is important to note that vasodilators that reduce wave reflection (such as calcium channel blockers) have been shown to reduce cognitive decline in older adults with systolic hypertension.\textsuperscript{3,4,17} It is possible that novel agents that reduce systemic wave reflection may be beneficial, particularly if they do not reduce cerebrovascular resistance. Although the ultimate therapeutic goal should be to reduce aortic wall stiffness, achieving this goal will require a much deeper understanding of the cellular and molecular mechanisms that lead to arterial stiffening with aging and disease.

Considerations about hemodynamic differences in specific vascular beds are also relevant for the interpretation of the study by Cooper et al. In this study, the authors measured microvascular function in the forearm, which, by virtue of being a high-resistance vascular territory at rest, may exhibit a microvascular bed that is relatively protected from the ill effects of proximal arterial stiffening. Therefore, the mediating effect of microvascular dysfunction on cardiovascular risk measured in this territory might have underestimated the true mediating effect of microvascular damage/dysfunction in high-flow target organs such as the brain and the kidney. For instance, recent data from the Age, Gene/Environment Susceptibility-Reykjavik study suggest that an important proportion of the relationship between aortic stiffness and glomerular filtration rate is mediated by renal microvascular function.\textsuperscript{13}

Some additional considerations are worth mentioning. The authors studied a composite end point of events, whereas microvascular dysfunction may be particularly relevant for specific end points (such as renal failure and dementia). As specific disease events accumulate in this cohort during follow-up, it will be interesting to assess the relationship between aortic stiffening, microvascular dysfunction, and incident disease. Finally, the effects deduced from the applied mediation analyses constitute, in a strict sense, a statistical rather than a mechanistic inference. Mediation analysis is a special type of multivariable modeling, which may be influenced by epiphenomena affecting both vascular measures (carotid–femoral pulse wave velocity and hyperemic microvascular blood flow), without necessarily implying that microvascular dysfunction participates in the causal pathway between large artery stiffness and cardiovascular events. However, the proposed effects are plausible and concordant with our current mechanistic understanding of arterial hemodynamics. Cooper et al should be congratulated for addressing an important mechanistic question with the use of relevant physiological measurements in the setting of a large, well-designed population study. The unprecedented availability of cardiovascular imaging techniques to characterize arterial function, flow, geometry, and wall properties, in tandem with microvascular function, tissue perfusion, and early signs of disease in target organs, should provide exciting opportunities to further advance our understanding of the macrovascular–microvascular cross talk and its role in the pathogenesis of cardiovascular disease in population studies and mechanistic clinical trials in humans.
3  Chirinos  Aortic Stiffness and Microvascular Disease


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Large Artery Stiffness, Microvascular Function, and Cardiovascular Risk
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