Stiff Arteries, Stiff Ventricles
Correlation or Causality in Heart Failure?
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The biophysical properties and neurohormonal regulation of arterial function are influential mediators of cardiovascular disease. Over the past 3 decades, the prognostic importance of arterial stiffness, as a measurable indicator of arterial function, has been recognized in both unselected populations and among patients with cardiovascular risk factors. Although there is a correlation between vascular stiffness and outcomes, the temporal and causal interrelationships with aging, hypertension, atherosclerosis, and the progression to heart failure are not fully understood. Aortic stiffening increases systolic load on the left ventricle (LV) contributing to ventricular hypertrophy and leading to increased myocardial oxygen demand, as well as indirectly promoting coronary disease and impaired perfusion.1 Arterial stiffness and wave reflection effects augment systolic blood pressure and place additional mechanical load on the heart leading to diastolic dysfunction and myocardial fibrosis.2,3 Increasing vascular stiffness precedes the onset of hypertension and may promote alterations in wall stress that accelerates atherosclerosis.4 This body of evidence has generated renewed interest in discovering whether arterial stiffness is more than a correlated risk factor and if it could play a role in the causative pathway to adverse cardiovascular events.

See Article by Ohyama et al

The proximal elastic arteries serve as capacitance vessels that distend to accommodate the stroke volume as it is transferred from the heart to the circulation and maintain efficient coupling with the mechanical properties of the myocardium.5 During systole, a pulse wave is propagated along the aorta that travels at a velocity that is an accurate surrogate for arterial stiffness.6 With advancing age, elastin fibers in the tunica media become degraded and fragmented leading to a less compliant collagen-dominant state with an associated rise in pulse wave velocity (PWV) and reflected pressure waves. Endothelial dysfunction plays a pivotal role in the progression to heart failure with neurohormonal interactions between the myocardium and the endothelium driving unfavorable outcomes.7 Genetic factors are also influential but, although the heritability of carotid-femoral PWV is ≈40%, the genetic variants that independently influence vascular stiffness are not well defined.8 An important unanswered question in cardiovascular medicine is what role aortic stiffness may play in the initiation of myocardial dysfunction and subsequent progression to heart failure in the general population.

In this issue of Circulation: Cardiovascular Imaging, Ohyama et al9 explored the relationship between aortic PWV and LV function using phase contrast imaging and strain analysis of tagged cardiac magnetic resonance imaging in a large multiethnic cohort. Age-related changes in proximal aortic stiffness have previously been associated with LV mass and concentricity independent of central blood pressure and conventional cardiovascular risk factors.10 New data of Ohyama et al9 indicate that higher aortic arch PWV is also associated with impaired circumprefugal systolic strain and diastolic function in a community-based population. This study provides further evidence implicating aortic stiffness in adverse cardiac remodeling and impaired myocardial function. A previous longitudinal Multi-Ethnic Study of Atherosclerosis (MESA) study investigated 5960 participants using radial artery tonometry and found that the magnitude of wave reflections was strongly predictive of new-onset heart failure, but did not assess PWV itself.11 It has been argued that systolic load ultimately determines LV remodeling, and the indirect effects of aortic mechanical properties are of secondary importance, but measures of aortic stiffness are also relatively less confounded by the degree of LV dysfunction.12 A Framingham cohort study of 2539 middle-aged to elderly adults followed up for a median of 10.1 years reported that carotid-femoral PWV was associated with an increased risk of incident heart failure—and comparable risk was conferred by PWV in patients with heart failure with either preserved or reduced ejection fraction.13 These data would suggest that, as there is no treatment for heart failure with preserved ejection fraction of proven benefit, modulating vascular function may be a promising target for intervention.14

Recent observational longitudinal data, also from the same MESA investigators, suggest that blood pressure control may be effective in halting the progression of aortic stiffening and breaking the vicious circle between hypertension and vascular aging.15 Measurement of aortic wall stiffness could provide a sensitive indicator for the initiation of vascular disease, but interventional studies have yet to determine whether a lowering of PWV leads to a reduction in cardiovascular events independent of alterations to classical risk factors.16 Endothelial cells are mechanosensitive and directly respond to stiffening of the extracellular matrix leading to enhanced permeability.
and uptake of cholesterol into the vessel wall. Endothelial dysfunction is not irreversible, and many emerging nonpharmaceutical and pharmacological therapeutic strategies are under investigation that aim to reduce oxidative stress and promote nitric oxide release. The observational study of Ohyama et al., taken with other longitudinal data, provides supportive evidence of the role that declining arterial elasticity may have in the development of subclinical impairment of both systolic and diastolic functions.

There are many approaches and technologies used to assess vascular stiffness that present both challenges and opportunities for advancing our understanding of hemodynamic factors in heart disease. In the study of Ohyama et al., the velocity of the propagating systolic wavefront in the aorta was determined using phase contrast imaging—a noninvasive approach for assessing vascular stiffness that offers good agreement with intra-aortic pressure measurements. Phase contrast imaging depends on adequate temporal sampling of the flow waveform particularly when model-fitting the systolic upstroke to minimize the influence of wave reflection effects. The most relevant blood pressure metric is also debatable as, although 24-hour ambulatory monitoring may better represent the cumulative exposure to hypertension, transient changes in vascular stiffness also occur with acute variations in blood pressure. Another factor not addressed in this study is the variation in elastic properties of the aorta as the pulse wave travels distally, as both extracellular matrix composition and expression of vascular disease vary in different territories. A limitation of the tagged deformation imaging used is the absence of data on long-axis function that is an independent predictor of survival, after adjustment for clinical variables and short axis function, in patients with heart failure. It would be appealing to combine complementary cardiac magnetic resonance data sets from the MESA cohort, including feature-tracking for strain assessment in each axis, to establish a comprehensive picture of longitudinal adaptations in LV mass, function, and aortic stiffness—findings that may not always be congruent with cross-sectional associations. The right heart is also an important determinant of outcome in heart failure, and there is emerging evidence that a similar relationship exists between pulmonary artery stiffness and right ventricular function to that observed in the systemic circulation.

Convincing data are still required on the putative feedback mechanisms between aortic and ventricular dysfunction, what processes might initiate and amplify the progression to heart failure in the general population, or any certainty as to whether outcomes in heart failure may be improved by modifying aortic elasticity independent of conventional risk factors. Pharmacological approaches to treat vascular stiffness, including angiotensin-converting inhibitors and calcium channel blockers, have achieved only modest results but there are promising data that Rho kinase inhibition, including pleiotropic actions of statins, may prevent atherosclerosis caused by vessel wall stiffening. Aortic PWV improves risk stratification independently of conventional cardiovascular risk factors, but its clinical value will ultimately depend on whether it can be proven to guide treatment and improve outcomes.

Disclosures

None.

References


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