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Late Arterial Waves: An Early Warning System for Heart Failure?

Naomi M. Hamburg, MD, MS

The heart and arterial tree are conjoined in the circulatory system—a concept taught in introductory physiology. Yet, our clinical paradigm for heart failure focuses predominantly on alterations in left ventricular structure and function.[1] There is growing interest in the interplay of vascular and cardiac dysfunction in the development of heart failure. With the parallel trends of increasing obesity and an aging population, there has been a linked rise in arterial stiffness and heart failure. Clinically symptomatic heart failure poses a significant burden to patients and the medical system. Prior to the expression of overt heart failure, there is a prolonged period of risk that provides a window for interventions to alter the disease trajectory. Identifying the arterial maladaptations that contribute to heart failure may expedite discovery of novel treatments. Importantly, early detection of vascular precursors to heart failure holds promise to target preventive therapies.

The advent of noninvasive arterial assessment has greatly facilitated our understanding of cardiac and vascular connections. Aortic stiffness can be measured by use of tonometry to determine pulse wave velocity. Arterial waveform evaluation has been used to estimate wave reflection as an evaluation of hemodynamic load.[2] Arterial stiffness and heart failure share multiple risk factors. Altered arterial function has been observed in the setting of established heart failure.[3] In patients with heart failure, higher central arterial stiffness measured by pulse wave velocity predicts mortality.[4] Arterial stiffness predicts the development of systemic hypertension and cardiovascular events.[5–7] A recent meta-analysis of over 17 000 participants confirmed the value of aortic pulse wave velocity beyond blood pressure measurements for predicting coronary heart disease, stroke, and composite cardiovascular disease events.[8] In longitudinal analysis including measurement of both central pressure and flow, forward pressure wave amplitude (a measure of proximal aortic properties) predicts a composite outcome of incident cardiovascular events that included heart failure.[9] Wave reflection estimated from arterial pressure waveform analysis alone (without concomitant flow assessment) has been shown to predict the risk of incident heart failure.[10] In patients with chronic renal insufficiency, carotid-femoral pulse wave velocity but not central pressure predicted incident heart failure hospitalizations.[11] Together these prior studies emphasize the critical intersections of arterial aging with cardiovascular end-organ damage and suggest the possibility that non-invasive arterial tests may have clinical utility in risk assessment.

Arterial stiffening alters both systolic load and the loading sequence of the left ventricle. Heightened wave reflection is a complex process determined by many factors including central stiffening, cardiac dysfunction, and peripheral impedance mismatch. Earlier and greater wave reflection differentially increases late systolic load. In animal models, late systolic loading conditions produce adverse ventricular remodeling and impair diastolic properties.[12,13] In cross-sectional studies in humans, higher late systolic load relates to impaired early cardiac filling, a marker of diastolic dysfunction.[14,15] Thus, a late-predominant loading sequence related to arterial dysfunction may impair cardiac dysfunction setting the stage for heart failure.

In the current issue of *JAHA—Journal of the American Heart Association*, Chirinos and colleagues report their findings from an investigation of the arterial loading sequence and incident heart failure events in over 6000 participants in the Multi-Ethnic Study of Atherosclerosis.[16] Peripheral arterial waveforms were measured using radial tonometry and used to calculate central pressure waveforms using a transfer function. The relative predominance of late to early systolic pressure was quantified as the ratio of the central pressure-time integral during the last third of systole compared with the first two-thirds of systole. Heart failure events were physician adjudicated based on standard criteria but did not distinguish between heart failure with preserved ejection fraction compared with reduced ejection fraction. The authors

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From the Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA.

Correspondence to: Naomi M. Hamburg, MD, MS, Section of Cardiology, Boston Medical Center, 88 East Newton St., Boston, MA 02118. E-mail: nhamburg@bu.edu

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found that a higher late to early central pressure ratio predicted incident heart failure in models adjusting for risk factors including blood pressure. Late systolic pressure predominance remained associated with heart failure events when accounting for augmentation index. There was evidence of predictive model enhancement by the late/early central systolic pressure ratio with higher c-statistic, 24% net reclassification index, improved integrated discrimination index, all suggesting the possibility of clinical utility in determining individuals at greater risk for heart failure. Further, later loading sequence was associated with higher risk of heart failure even in the absence of systemic hypertension.

The study findings refine our knowledge regarding links between cardiac and vascular dysfunction. The prospective investigation provides evidence that the time sequence of arterial systolic loading contributes to the development of heart failure. A favorable ventricular-arterial interaction is characterized by an early systolic predominant arterial pressure pattern.

Conversely, late pressure predominance during systole is a marker of adverse ventricular loading. Late systolic loading forces the ventricle to push uphill throughout systole and may contribute to ventricular maladaptative remodeling. A simple ratio-based metric from a non- invasive arterial waveform identifies individuals at risk to progress to clinical cardiac dysfunction.

It is worth considering in detail the interpretation of an elevated late to early systolic central pressure ratio. The authors attribute this waveform pattern as late systolic hypertension attributable to wave reflection alone without contribution from proximal aortic properties. The determinants are likely more complex. First, it is key to note that the authors used a ratio measure not a direct assessment of late systolic pressure. As is apparent from the representative waveforms provided, 2 changes–lower early systolic wave and higher late systolic wave–both will result in a higher late-to-early ratio. Lower early systolic pressure-time integral may reflect subtle impairments of left ventricular contraction and relaxation leading to an attenuated peak ejection rate that reduces early systolic pressure and prolongs the systolic ejection period.[17,18] Second, multiple factors contribute to the apparent wave reflection that creates a higher late systolic pressure wave. A higher forward wave amplitude related to proximal arterial stiffening and a prolonged systolic duration of the forward wave both magnify apparent wave reflection and contribute to late systolic hypertension.[19] Radial tonometry limits assessment to pressure waveforms without direct flow measurement; therefore, the relative contribution of forward and backward wave to the overall waveform cannot be distinguished. Third, central pressure waveforms were derived from radial waveforms using a transfer function that depends on assumptions that may not be accurate across all participants.[20] Carotid pressure waveforms may have enhanced accuracy for determining central pressure. Finally, altered loading sequence may have differing relations with diastolic as compared with systolic function. Studies evaluating heart failure with preserved versus reduced ejection fraction or including longitudinal myocardial evaluations will be helpful in this regard. Thus, the observation that relative late systolic hypertension represents an unfavorable pattern is a starting point for additional studies, particularly with detailed arterial assessments that include measurements of both pressure and flow. It would be premature to conclude that reducing peripheral wave reflection—not central aortic stiffness—is the most appropriate treatment target for heart failure prevention.

The present study emphasizes the relevance of arterial dysfunction and abnormal loading sequence to heart failure. A simple arterial evaluation such as measuring late wave predominance may prove valuable as an early detection system for individuals at risk for heart failure. A more precise physiologic assessment of the relative importance of central arterial stiffening, left ventricular properties, and peripheral arterial compliance is required prior to selecting approaches for intervention to preserve cardiac function. As our concept of heart failure expands to cardiovascular failure, our therapies will undergo parallel expansion.

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Disclosures

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