Impedance Progress
Aortic Diameter Rears Its Head Again?

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Changes in global arterial function and blood pressure pulsatility play an important role in the exponential increase in the incidence of various common afflictions of aging. However, our current approach to hemodynamics, evaluating the peak (systolic blood pressure) and trough (diastolic blood pressure) of the blood pressure waveform in the arm, provides a limited view of pulsatile hemodynamics. As a first refinement, blood pressure can be separated into steady-flow and pulsatile components, mean arterial pressure (MAP) and pulse pressure (PP), respectively. Numerous recent studies have shown that many serious clinical events may be more closely linked to PP, which is related to large artery stiffness, rather than MAP, which is determined by small artery function and cardiac output. However, systolic blood pressure or PP in the arm probably does not tell the full story. Conventional brachial systolic blood pressure represents a variable composite of PP (large arteries) and MAP (small arteries), depends on ventricular ejection characteristics and arterial properties, and, because of transmission delays and wave reflection, may not be fully representative of central aortic pressure, which may be more relevant to cardiac and cerebral function. These additional sources of variability may have important implications for the pathogenesis of cardiovascular disease and response to treatment.

The study by Segers et al in the current issue of Hypertension represents an important step forward in our quest to quantify the effects of regional arterial function on the pathogenesis of cardiovascular disease in the community. The authors are reporting pulsatile hemodynamics from the first round of evaluations in a planned longitudinal, observational study of >2000 initially healthy men and women between 35 and 55 years of age recruited from 2 adjacent communities in the suburbs of Brussels, Belgium. The Asklepios investigators assessed pulsatile hemodynamics using a noninvasive approach first developed by Kelly and Fitchett2 and used extensively in recent years by our research group.3,4 Central pressure is assessed by direct carotid tonometry. Aortic flow is assessed by measuring Doppler velocity in the left ventricular outflow tract and multiplying by cross-sectional area to give volume flow. Pressure and flow are then analyzed together to compute aortic input impedance, which provides a comprehensive assessment of regional and global arterial properties. Key pulsatile hemodynamic variables derived from these analyses include characteristic impedance (Zc), which is the pulsatile pressure–flow relation of the proximal aorta, total arterial compliance (C), and estimates of forward and reflected wave amplitude and timing. In addition, conventional hemodynamic variables are obtained, such as cardiac output, stroke volume, and peripheral vascular resistance. Carotid femoral pulse wave velocity (PWV), which is closely related to aortic wall stiffness, is also assessed. Using this approach, it is possible to determine the anatomic and physiological correlates of abnormal blood pressure with reasonable precision.

One goal of the present analysis was to evaluate differences in various measures of “arterial stiffness.” Arterial stiffness is a descriptive phrase that may connote increased propagation velocity (PWV), increased impedance to volume flow (Zc) or reduced capacity to store blood (reduced C or, alternatively, increased volume elastance [1/C]). The foregoing functional measures of arterial stiffness (PWV, Zc, and volume elastance) share similar relations to arterial wall stiffness but have markedly differing degrees of inverse sensitivity to diameter. PWV is relatively insensitive to diameter, whereas Zc and volume elastance are highly dependent on diameter. As a result, these “stiffness” measures may change divergently if diameter changes. By measuring the full complement of stiffness measures and looking for disparate change, one can estimate the relative contributions to arterial stiffening of changes in the material properties of the arterial wall versus changes in lumen diameter.

The Asklepios investigators found that MAP and peripheral resistance increased between the ages of 35 and 55 years. Peripheral PP increased in women but was unchanged in men. PWV, augmentation index (AI), and global reflection increased with age in men and women, whereas Zc was unchanged in women and actually fell modestly in men. Thus, as discussed in the article, there was an apparent discrepancy between increasing PWV and stable or falling Zc, suggesting that an increase in diameter accompanied aortic wall stiffening. In addition, stroke volume, C, Zc, and AI were found to be major correlates of central PP, approximately in that order.

The Asklepios findings at once confirm the importance of aortic diameter as a key determinant of aortic functional properties and yet seem to conflict with our earlier finding that elevated PP in relatively healthy middle-aged-to-elderly patients with systolic hypertension was associated with increased Zc and reduced effective aortic diameter.4 However, it is important to note that the mean age in our previous study was 15 years older than Asklepios (60 versus 45 years), and the hypertensive patients in our study had markedly elevated PP as compared with the relatively healthy Asklepios par-
PP increases and AI stabilizes or falls (Figure). Thus, the wave amplitude increases after age 60 years, at a time when PWV and AI. In contrast, in collaboration with colleagues years of age, when PP is relatively stable despite an increase wave amplitude change relatively little between 35 and 55 years, with little change in Zc and PP. In contrast, after this age, previous studies have shown that MAP and AI continue to increase, implying an increase in Zc (or a decrease in C), although this has not yet been assessed comprehensively in a broad community-based sample. Note that many stiffness measures have nonlinear relations with age, with a transition at ~55 years of age. As a result, extrapolation of observations before age 55 years (tangent arrows) may lead to erroneous conclusions regarding hemodynamic changes in the elderly.

The Asklepios investigators found that Zc and forward wave amplitude change relatively little between 35 and 55 years of age, when PP is relatively stable despite an increase in PWV and AI. In contrast, in collaboration with colleagues at the Framingham Heart Study, we have shown that forward wave amplitude increases after age 60 years, at a time when PP increases and AI stabilizes or falls (Figure). Thus, the age-related increase in PP and associated increase in prevalence of isolated systolic hypertension beyond 60 years of age represents a dramatic reversal of the earlier patterns seen in the Asklepios cohort. These simple observations suggest that, as with any study, extrapolation of the Asklepios results beyond the studied age range is not advisable (Figure).

The Asklepios study highlights a number of important questions to which we do not presently have full answers. Does aortic lumen area actually increase in the age range studied or is the differential change in Zc and PWV indicative of regionally distinct change in arterial properties? As noted in the article, geometric implications of differential changes in Zc and PWV are based on the assumption that the 2 variables are measured in the same location. Because Zc is related to proximal arterial properties, whereas carotid–femoral PWV evaluates spatially averaged properties of a diverse segment of descending aorta and iliacs, differential changes in Zc and PWV may represent differences in regional stiffness rather than geometry.

If present, is the increase in aortic diameter pathologic, because of elastin fragmentation and loss, or passive, because of the observed increase in MAP? If the latter, when MAP stops rising at approximately age 60 years, does diameter passively stabilize, leading to an increase in Zc and PP as the aortic wall continues to stiffen? Alternatively, is the early increase in diameter active and compensatory rather than passive or pathologic, serving to stabilize PP as the aortic wall stiffens? Does this compensatory “outward remodeling” of the aorta reach a limit at some level of diameter or age in certain individuals, after which PP increases as wall stiffening outpaces the increase in diameter? Beyond a certain age or in some individuals, do other factors (inflammation, obesity, or genetics) contribute to active smooth muscle cell hypertrophy or interstitial fibrosis in the aortic wall, simultaneously promoting increased wall stiffness while limiting further enlargement or actually reducing aortic lumen area? How much of a role does intimal thickening or dysfunction play? Do pathways that normally transduce aortic flow (endothelium) or effect changes in aortic diameter to maintain matching between flow and diameter fail with advancing age or in the presences of certain risk factors, leading to increased pressure pulsatility despite constant or falling flow?

The present Asklepios data set spans an age range that precedes the hemodynamic transition from a pattern of increasing peripheral resistance, MAP, and AI at relatively constant cardiac output and PP to a pattern of rapidly increasing PP with limited change in MAP and reductions in AI and cardiac output later in life. This abrupt hemodynamic reversal underlies the concurrent transition from predominant diastolic or mixed hypertension to overwhelmingly predominant isolated systolic hypertension in older people. Clearly, extrapolation of trends observed in the present Asklepios data beyond the age range studied cannot yet answer the foregoing open questions regarding the hemodynamics of increased PP in the elderly. However, in light of the rich set of baseline impedance data obtained by the Asklepios investigators, we eagerly await the results of future evaluations in this interesting cohort.

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References
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