Editorial Commentary

Pathogenesis of Elevated Peripheral Pulse Pressure
Some Reflections and Thinking Forward

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“Ashes to ashes, dust to dust, if the cancer don’t get us, the arteriosclerosis must”
—Richard Gordon in The Alarming History of Medicine, 1993

Substantial evidence suggests that arterial remodeling evolves over a life course under the conjoint influence of genes, environmental factors (including vascular risk factors), and lifestyle characteristics (such as diet and physical activity). Such arterial remodeling involves multiple vascular territories and is panarterial, ie, it involves all layers of the arterial wall. More recently, considerable attention has focused on the physiological aspects of propagation of blood within the aorta, and several important concepts have evolved. The aorta is no longer regarded as just a passive conduit that transports blood to the vital organs. Rather, it is a complex organ that remodels in dynamic fashion in response to biomechanical stresses that accumulate over the life course. The different segments of the aorta vary in their relations to risk factors, underscoring the heterogeneity in remodeling characteristics across the arterial tree. Second, age-associated changes in the aortic wall include fragmentation of the elastin fibers, increased synthesis of collagen, and calcification. The molecular epidemiology of these vascular remodeling changes have been well characterized, and are complex, being mediated via the interaction of vascular smooth muscle cells, integrins, metalloproteinases, endothelial function, and the renin-angiotensin axis, inflammation, and other pathways. Third, vascular flow propagation is the combination of steady flow (mean arterial pressure) and pulsatile (pulse pressure) components. The proximal (central) aorta stiffens with age, and these changes are associated with an increase in the pulsatile component (increased central pulse pressure), which in turn places a burden of increased afterload on the left ventricle. There is widespread agreement that elevated pulsatile load is associated with increased risk of cardiovascular disease, including myocardial infarction, stroke, and heart failure. Fourth, peripheral pulse pressure measured at the level of the brachial artery does not adequately portray the “pulsatile load actually faced by the heart,” ie, central pulse pressure. Therefore, investigators have used different noninvasive techniques to better characterize central pulse pressure.

Controversies Surrounding the Origin of Higher Pulse Pressure in Older People and in Hypertension

Despite the overwhelming scientific consensus regarding the concepts noted above, controversies plague the mechanisms contributing to the pathogenesis of age-related increases in pulse pressure. Understanding the biological underpinning of increases in central and peripheral pulse pressure are critical because these changes underlie the pathogenesis of isolated systolic hypertension in the elderly, which is the most common form of hypertension in the community. The theory of flow propagation suggests that a forward pressure wave (also called the incident wave) is generated by the initial force of ventricular systole. This forward pressure wave is transmitted along the viscoelastic aortic tube until it encounters branch points and peripheral resistance, which represent zones of impedance mismatch (Figure, Panel I). At such transition zones, the forward wave turns backwards as a reflected wave. The reflected wave travels retrograde toward the heart only to encounter the forward pressure wave, on which it falls thereby generating a summed or augmented pressure wave. Because the reflection points are closer to the peripheral arteries, we observe “pulsatile amplification” of the pulse wave (Figure, Panel II), and consequently peripheral pulse pressure may overestimate central pulse pressure in younger individuals.

There is widespread agreement that the concept of vascular stiffness likely reflects the combined effect of 3 components: characteristic impedance of the central aorta (Zc, which determines pulsatile pressure-flow relations), pulse wave velocity, and total arterial compliance (Figure, Panel I). There is also an acceptance of the fact that all 3 components of vascular stiffness change unfavorably with age: a decrease in compliance accompanies increased characteristic impedance and higher pulse wave velocity. The central issue of controversy is the debate on the relative contributions of the reflected wave versus the incident wave to the genesis of higher peripheral pulse pressure.

A classic long-held view, supported by O’Rourke et al, has been that with aging, the increase in aortic stiffness translates into an increase in pulse wave velocity. As a result, the reflected wave travels back faster and “overlays” the forward wave earlier in systole, and therefore “augments” the central pulse pressure considerably (Figure, Panel III). In
other words, wave reflection is the principal cause of higher pulse pressure in older people.

A more recent view, espoused by Mitchell, has challenged this classical view and raised the possibility that elevated pulse pressure in the elderly and in hypertension may largely be the result of impedance mismatch at the very proximal part of the aorta, ie, a smaller effective aortic diameter, with wave reflection playing a more minor role. Such a view is supported in part by some cross-sectional studies reporting inverse association of peripheral pulse pressure and aortic diameter measurements. However, other reports have noted positive associations of systolic or diastolic pressures with aortic diameter.

The theory proposed by Mitchell has been challenged by O’Rourke et al on both technical and theoretical grounds. The technical objection relates to issues surrounding the determination of the timing of the reflected wave, which depends on the identification of an inflection point on the pressure waveform. The theoretical objections include controversies surrounding the use of a water hammer formula (an equation valid in systems without reflections) for calculating effective aortic diameter, and around estimates of the effective reflecting distance in older people; the classic view suggests a shorter reflecting distance but the opposing view notes an increase in this distance with age. There is also a lack of clarity on age-associated changes in characteristic impedance. A study based on individuals between 35 and 55 years of age reported a decrease in Zc with age in men and no change in women, conflicting with Mitchell’s observations of a higher Zc in middle-aged to elderly women. Yet another study used the ratio of pressure harmonics to flow harmonics to show that aortic input impedance increases with age.

Is the aforementioned debate or controversy important to resolve? The answer would seem “yes” because the relative contributions of central aortic impedance versus wave reflection to the development of a higher pulse pressure may have therapeutic implications. For instance, if higher pulse pressure was attributable to early wave reflection, agents such as low doses of nitrates and arterial vasodilators may be more suited because they eliminate late systolic augmentation by virtue of arterial dilation and “trapping” of reflected waves in the periphery, an effect achieved without altering peripheral resistance at doses used. On the other hand, if increased central aortic impedance is largely responsible for higher pulse pressure, agents such as cross-link breakers (such as alagebrium) or vasopeptidase inhibitors may be preferred.

Is a Resolution of the Controversy Imminent?

In this issue of Hypertension, Mitchell and colleagues attempt to lay this controversy to rest by directly measuring aortic diameter, aortic stiffness, pulse wave velocity, and the augmentation index in a moderate-sized sample of patients with hypertension using state-of-the-art methods that directly tackle some of the criticisms noted above. The authors demonstrate via statistical modeling that higher pulse pressure is associated with greater aortic wall stiffness, a smaller aortic root diameter, and a higher augmentation index (results of models using pulse pressure as a continuous variable).
They use two different methods of estimating the augmentation index, including one independent of the identification of the inflection point on the forward wave. They use impedance spectra to infer that characteristic impedance is increased more in individuals with higher pulse pressure but wave reflection is not.

Several caveats about this study warrant attention before accepting the thesis that these data support a primacy of a relatively smaller proximal aortic diameter over the reflected wave in the pathogenesis of higher pulse pressure. The study sample investigated middle-aged to older patients with mixed patterns of hypertension (both isolated systolic and systolodiastolic hypertension were represented). The chronicity of hypertension is not reported; so it is not clear whether the observed cross-sectional associations are causal, or if they represent the effects of long-standing hypertension on arterial wall properties, or if the changes in vascular properties are a concomitant of hypertension itself. Further, it is unknown whether interindividual variation in aortic root diameter influences the propensity to develop systolic hypertension or higher pulse pressure later in life. Only a prospective study design could clarify this. Additionally, it is difficult to gauge the relative contributions of a small aortic root diameter versus the augmentation index without knowledge of the partial R squares for these variables in the final statistical model (model 3 in Table 313). Moreover, it is not clear whether the data presented here are generalizable to community-dwelling individuals with predominantly isolated systolic hypertension, to those without hypertension, or to older people with lesser degrees of elevation of pulse pressure. Also, it should be noted that the relations of systolic and diastolic blood pressure to aortic diameter vary across different aortic segments2,13 and are inconsistent in the published literature as noted earlier.2,5,7 Furthermore, other investigations have demonstrated positive associations of carotid artery diameter with pulse pressure in hypertensive individuals, with a reduction of arterial diameter (along with intimal medial thickness) being observed when blood pressure is lowered; this direct relationship between carotid diameter and treatment effects seem to be related more to lowering of local (carotid) pulse pressure.14 Thus, the relationship observed by Mitchell et al in their report seems to conflict with several other reports in the literature.

An alternative conclusion from the data in the current report13 is that perhaps peripheral pulse pressure is determined both by central aortic properties and by wave reflection. The debate then narrows down to a question of the relative contributions of the two theories/mechanisms. Clearly, such contributions may vary across study samples, with gender or with age, height, and obesity, a possibility raised by data evaluating different subgroups within the study sample in the current investigation.13

Perspectives
Perhaps the two theories are not mutually exclusive, and the ongoing debate, although of pathophysiological importance, distracts from other important unanswered questions in pulsology. For instance, it is not quite clear whether central pulse pressure provides incremental clinical value over peripheral pulse pressure for predicting cardiovascular outcomes, howsoever intuitive the advantages of measuring central pulse pressure may seem. Results of some of the studies comparing the utility of central versus peripheral pulse pressure have not been consistent.25,16 It is also not established whether treatment strategies directed at lowering elevated vascular stiffness (either mediated via greater characteristic impedance or by greater wave reflection) are superior to approaches that simply target blood pressure. Fortunately, we do know some of the factors that favorably influence arterial stiffness. These include lifestyle-related and other measures such as exercise, weight loss, low-salt intake, moderate alcohol consumption, and fish oil intake.

The article by Mitchell et al in the current issue of the Journal adds some clarity to the ongoing debate regarding what causes a high pulse pressure, but it is unlikely to resolve it completely. Meanwhile, it seems clear that treating and controlling elevated systolic pressure in people with hypertension (with currently available blood pressure-lowering medications that work well) need not wait for these controversies to be resolved.

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