Triangulating the Peaks of Arterial Pressure

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Increased arterial stiffness and excessive pressure pulsatility have emerged as important risk factors for a number of common disorders of aging, including cardiovascular disease, stroke, cognitive impairment, and renal disease. The triple-threat combination of robust associations between arterial stiffness and the foregoing disorders, a marked increase in arterial stiffness with advancing age and the graying of our society, has led to intensive efforts to identify mechanisms that contribute to arterial stiffening and widening pulse pressure to define interventions to prevent or reverse stiffness and potentially reduce the substantial burden of related disease.

Wave reflections complicate the task of evaluating arterial hemodynamics and play an unclear role in the foregoing diseases. When the heart ejects, ventricular outflow interacts with characteristic impedance of the proximal aorta to produce the forward pressure wave, which travels down the normally compliant aorta at a finite pulse wave velocity (PWV). When the forward wave encounters impedance mismatch, such as a branch point or a change in diameter or wall properties, a partial reflection occurs. Innumerable reflections arising from locations distributed throughout the arterial tree summate into a remarkably discrete reflected pressure wave with amplitude \( \approx 40\% \) of the incident wave. The summated reflected wave returns to the central aorta in mid systole, creating an inflection point and secondary late systolic pressure rise that often augments central aortic systolic and pulse pressure. Variable timing of this retrograde-traveling reflected wave creates regional inequalities in systolic and pulse pressure and, therefore, complicates interpretation of single point pressure measurements, such as standard brachial blood pressure, which may differ from central aortic pressure.

Augmentation index (AI), which expresses late systolic pressure augmentation as a percentage of pulse pressure, is frequently used to assess wave reflection (Figure). AI, which depends on both timing and amplitude of the reflected wave, has also been widely cited as a measure of arterial stiffness based on the assumption that increasing PWV leads to progressively earlier wave reflections from a relatively fixed reflecting site. The resulting progressive systolic overlap of the forward and reflected wave has been proposed as the principal determinant of increasing pulse pressure with advancing age. However, recent community-based studies have challenged these seemingly straightforward assumptions. Timing of wave reflection is related to PWV and the distance to the “effective” reflecting site. A typical aortic PWV of 6 to 7 m/s and roundtrip reflected wave transit time of 120 to 150 ms suggests that the effective reflecting distance (ERD) is \( \approx 40 \) to 50 cm from the heart in healthy young women and men, respectively. However, rather than vary inversely with PWV, timing of wave reflection hovers in a relatively narrow range (110 to 150 ms) across the full human life span, despite a major (\( \approx 3\)-fold) increase in aortic PWV. Minimally changing reflected wave transit time in the presence of a marked increase in aortic PWV indicates that ERD increases substantially with age. ERD lengthens in children because of an increase in body size. In middle-aged and elderly individuals, ERD lengthens because the aorta, which is normally much more compliant than the muscular arteries, becomes as stiff as the muscular arteries by \( \approx 50 \) to 60 years of age. This “impedance matching” between aorta and muscular arteries reduces proximal wave reflection and shifts reflecting sites downstream. Loss of proximal wave reflection implies increased transmission of pulsatility into the periphery, potentially causing damage, unfavorable remodeling, and impaired flow reserve.

Because of the foregoing effects of age on timing and amplitude of wave reflection, AI has complex relations with age. AI falls slightly with growth during childhood, increases rapidly between 20 and 40 years of age, and then plateaus or falls beyond 60 years of age. In contrast, pulse pressure, aortic PWV, and forward wave amplitude increase modestly before 40 years of age and then dramatically after 60 years of age, when cardiovascular risk increases exponentially. Thus, excessive wave reflection is unlikely to explain a major component of age-related increases in pulse pressure. AI is lower in men than women and is reduced in the presence of obesity, diabetes, and higher heart rate, despite elevated PWV. AI is also lower in individuals with impaired left ventricular function despite normal or increased wave reflection, because the failing heart cannot augment pressure in the face of a late systolic increment in load. Accumulation of these risk factors with age may contribute to the plateau or fall in AI in the elderly. Complex relations with age and inverse relations with several major cardiovascular disease risk factors may limit the use of AI for risk stratification in the general population. Furthermore, dependency of AI on multiple factors has clouded our understanding of changes in wave reflection with advancing age.

In this issue of Hypertension, Westerhof et al describe a new tool that may help deconvolve some of the complex dependencies of AI on timing and amplitude of the reflected wave and duration and pattern of systolic ejection. The approach is straightforward and logical. To assess forward and reflected wave amplitude, pressure and flow waveforms are both required. When the reflected wave returns to the heart during systole, as is
generally the case, the forward and reflected waves summate, resulting in augmentation of pressure and deceleration of ventricular outflow. Based on examination of a series of studies performed using invasive catheter-mounted pressure and flow sensors, Westerhof et al. hypothesized that the shape of the truncated aortic flow waveform could be estimated by using a triangular pseudoflow waveform. The pseudoflow waveform is constructed by assuming 0 flow during diastole and connecting lines from 0 at the timing of the pressure waveform foot to some empirical maximum value at the estimated timing of peak flow and then back to 0 simultaneous with the dicrotic notch. Timing of peak flow was set equal to inflection point timing, signaling the foot of the reflected pressure wave. Alternatively, peak flow was assumed to occur at 30% of the ejection period. Measured pressure and pseudoflow waveforms are then used to separate forward and reflected wave components, of which the peak-trough amplitudes are easily assessed (Figure).

A major difference between AI and the Westerhof approach lies in the definition of the baseline used to compute the amplitude of the reflected wave. In the common situation where AI is >0, only the component of the reflected wave that projects above the forward wave horizon is considered, which effectively sets a horizontal baseline at the level of the forward wave peak (Figure). This approach suffers from a “tip-of-the-iceberg” phenomenon, because the bulk of the reflected wave is submerged along the falling edge of the forward pressure wave. In contrast, the Westerhof “triangulation” approach turns the pressure baseline on its side and thereby explores the full vertical amplitude of a reflected wave clinging to the falling edge of the forward wave peak (Figure). The Westerhof approach also considers diastole, where a substantial component of the reflected wave may be located in cases with a relatively late or broad reflected wave. In cases where the early forward wave peak is dominant (AI <0), AI provides essentially no information on reflected wave amplitude, per se, whereas the Westerhof approach is relatively insensitive to this transition from an augmented to a nonaugmented state. Thus, one would expect, and data presented in the article suggest, that the Westerhof approach offers a more robust estimation of reflected wave amplitude, free of the confounding effects of reflected wave timing (compare $R^2$ values in Westerhof Figure 4).

However, there are potential limitations to the new approach. The number of cases evaluated in this proof-of-principal article is small, and case selection bias (ie, an indication for cardiac catheterization) may have affected the results. Furthermore, the choice of a triangular flow wave-
form shape may have limitations. Effects of wave reflection on the central pressure and flow waveforms represent a compromise between pressure augmentation and flow deceleration. The settling point for this compromise depends on ventricular structure, function, and contractility. In cases where the ventricle is able to augment pressure, for example, a concentrically hypertrophied, pressure-loaded left ventricle, pressure augmentation will predominate over flow deceleration, and the falling edge of the measured flow waveform will be convex. Linear extrapolation to 0 of the falling edge of the pseudoflow waveform will, thus, underestimate true flow, and reflected wave amplitude will be overestimated. In other cases, for example, those with impaired ventricular function or extreme reflected wave intensity, deceleration of ventricular outflow will be accentuated, the flow waveform will be concave, and reflected wave amplitude will be underestimated. It seems that the latter scenario predominated in this small series of cases, because the slope of the relation between estimated and actual reflected wave magnitude is 0.79 to 0.82 in Westerhof Figure 4. This is probably a manifestation of the high levels of wave reflection in this small sample, with most cases having a reflection magnitude between 50% and 100% (Westerhof Figure 4), whereas values typically range between 30% and 50%.

The new technique proposed by Westerhof et al.10 and the traditional AI approach described by Murgo et al1 are complementary. The Westerhof approach offers a potential advantage in terms of estimating amplitude of forward and reflected waves free of the vagaries of variable overlap and an uncertain baseline for the reflected pressure wave. On the other hand, AI provides an integrated summary of the relations among reflected wave timing, amplitude, and ventricular function. For example, higher AI in the presence of typical mid-systolic timing and nominal reflected wave amplitude may be indicative of (rather than a cause of) ventricular hypertrophy. Conversely, low AI in the presence of increased reflected wave amplitude and early timing may be a sign of impaired ventricular function. When substantial central pressure augmentation is present, interventions that reduce wave reflection produce reductions in central systolic and pulse pressure that are generally underestimated by the change in brachial systolic and pulse pressure, because the reflected wave determines peak pressure in the aorta but not the arm.11 This important phenomenon might be overlooked if attention is focused on reflected wave amplitude without considering the associated change in central pressure augmentation. Regardless of which technique is used, it is important to emphasize that these derived measures of wave reflection are likely to have complex and potentially inverse relations with aortic stiffness. With this caveat in mind, triangulation will likely prove useful in our attempts to navigate the peaks of pulsatile hemodynamics.

Disclosures
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