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NOVEL USES OF OFFICE-BASED MEASURES OF ARTERIAL COMPLIANCE

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Abstract

Office-based blood pressure monitoring has been the primary way of managing the cardiovascular risk associated with a diagnosis of hypertension. As research unfolds the nature in which the pulse waveform is generated, additional insights beyond standard measures of systolic and diastolic blood pressure have emerged to help reclassify the cardiovascular risk of patients or point out patterns that have, in longitudinal cohort studies, shown promise as predictors of outcomes such as heart failure. In this review, we focus on the pressure profile in the proximal aorta that can be obtained easily and noninvasively from the radial or brachial artery during a clinical office encounter and the potential value of these measures in outcomes such as left ventricular hypertrophy and heart failure.

Introduction

The radial pulse has long been a source of input into medical decision making as witnessed by many treatises on the characteristics of pulse volume, contour, and rate. Hardening of the pulse was associated with excessive salt intake in early Chinese history, and pulse characteristics have traditionally been employed in characterizing various kinds of fevers and heart disease, particularly disorders of the aortic valve. In the 19th century, a number of clever devices, known as sphygmographs, were constructed that amplified and recorded the radial pulse contour. This enabled physicians to study pulse characteristics and note the relationship between changes in pulse contour and aging as well as diseases such as chronic kidney disease and left ventricular hypertrophy.[1] The Royal College of Physicians (London) adopted a picture showing the taking of the pulse as its logo. However, sphygmographs were impossible to calibrate as there was no known unit of pressure until 1896, when Riva-Rocci promulgated their use of the mercury manometer.[2] Within 10 years, Korotkoff's work on the sounds heard during cuff deflation using the Riva-Rocci approach made the measurement of systolic and diastolic pressure an office-based possibility.[3] In the next 25 years, the Insurance Companies of North America demonstrated that elevated levels of blood pressure reduced lifespan.[4] The sphygmographs were relegated to history, and attention focused on brachial blood pressure and then its treatment throughout the next century. The technique used to measure brachial blood pressure remained basically unaltered until mercury was phased out of clinical practice in the early 21st century. Currently, clinical management of hypertension continues to rely on office-based measures of systolic and diastolic blood pressure.

Re-emergence of the Pulse

Several phenomena occurred over the last 40 years that sparked renewed interest in the pulse wave contour.[5] First, arterial stiffness, measured as the velocity of pulse wave travel in the aorta, has emerged as an independent (of systolic blood pressure) predictor of mortality in 17 longitudinal studies involving more than 15,800 subjects.[6] Arterial stiffness is an important component of determining the manner in which the pulse wave navigates the circulatory bed. Next, there is increasing recognition that while medical management of hypertension may reduce cardiovascular outcomes, it does not entirely eliminate them, which raises the possibility of a need for improved brachial blood pressure management. In this regard, the Conduit Artery Function Evaluation (CAFÉ) study showed that despite equivalent brachial blood pressure reduction, differences in blood pressure at the level of the aorta, measured noninvasively by applanation tonometry, may be important for predicting outcomes in hypertension management.[7] Finally, there is the well-demonstrated but largely unappreciated phenomenon of pulse pressure amplification, which shows that as the pulse from each heartbeat enters the proximal aorta, its pressure excursion (systolic minus diastolic pressure; i.e., the pulse pressure) increases as the pulse travels through the circulation. The magnitude of this increase in pulse pressure is variable, mainly driven by the systolic pressure, and difficult to predict when armed only with knowledge of the brachial blood pressure values. For example, the Anglo-Cardiff Cardiovascular Trial (ACCT) in the United Kingdom showed considerable overlap of central systolic pressure when discrete levels of brachial blood pressure were measured; there was a 70% overlap in central systolic pressures in those with a brachial pulse pressure of 130 to 139 mm Hg (prehypertensive) compared to those with brachial systolic pressures of 140 to 149 mm Hg (stage 1 hypertension).[8]

Pulsology 101

Careful examination of standard radial pulse contour can underscore several points about the peripheral and central pulse. Figure 1 shows the radial pulse of a relatively healthy young subject studied as a normal control at our center. This waveform was obtained using applanation tonometry, a process whereby a handheld Millar tonometer is connected to a computer that senses pressure changes in the tonometer's tip and displays these

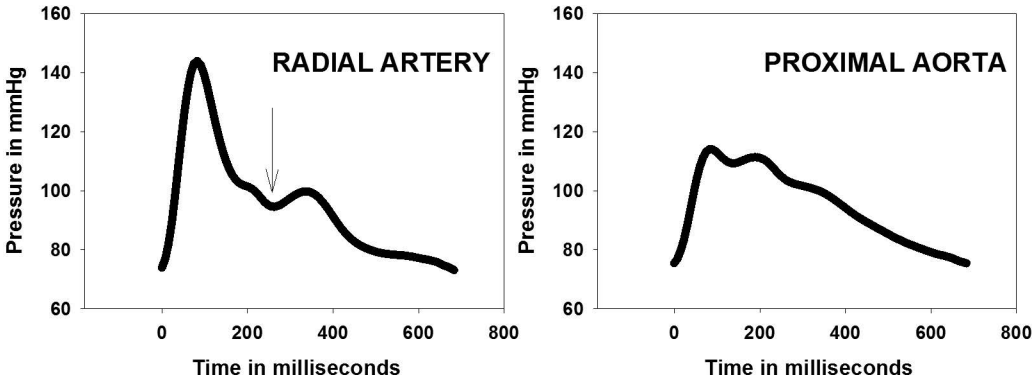

Figure 1. Left panel shows a radial artery pressure waveform obtained by applanation tonometry from a healthy 21-year-old patient. At the point shown by the downward arrow (around 270 ms), the aortic valve closes, which is called the "incisura." Right panel shows estimated proximal aortic pressure waveform derived using a general transfer function based on the radial artery waveform as input.[14]

in real time, calibrated by the brachial artery blood pressure. The tonometer is centered over the radial artery, and 10 seconds of visible radial waveforms are captured and averaged into a single reading. As shown in Figure 1, the radial waveform looks very similar to what you might see in an intensive care unit patient with an indwelling radial arterial line. The important things to notice about the arterial pulse in this healthy 21-year-old begin with a simple query. In Figure 1, at the point shown by the downward arrow around 270 milliseconds in the left panel, the aortic valve closes (known as the "incisura"). However, the pressure *rises* after this point, despite the isolation of the "pump" in the circulation. How can this be? The answer requires a brief review of the physics of wave propagation.

The pulse, like all waves, is subject to reflection. When the forward-traveling pulse wave travels in the circulation (after being initiated by left ventricular ejection), it meets several challenges that result in wave reflection. These include branch points, plaque, changes in vessel diameter, and changes in viscoelastic properties in the aortic wall that generate a series of echoes, or reflections, which summate and travel in the reverse direction back towards the aortic valve.[9,10] Like all waves, these backward-traveling waves add algebraically to the forward-traveling waves to yield additional systolic pressure. In health, when wave velocity is slow, the reflection backwards arrives in very late systolic or early diastole, producing the characteristic rise in systolic pressure *after* the incisura. Plausibly, this is a good thing as it augments early diastolic pressure, and since heart perfusion is mainly in diastole, it "primes the pump" for coronary perfusion.

With increasing arterial stiffness, as noted above, the velocity of pulse wave travel increases. This means that the reflected pulse wave arrives at an earlier time, now in late systole. To understand the significance of this finding, it will help to review a laboratory study of this phenomenon and examples of reflected pressure wave magnitude and late systolic loading we have recently observed in the Multi-Ethnic Study of Atherosclerosis.

Late Systolic Loading is a Bad Thing

To follow the logic here, bear with me while I present a bit of rodent data on early versus late systolic loading from our colleagues in Japan. In an elegant study of this concept, Kobayashi and colleagues used a rodent model in which they banded the aorta in rats and created a situation where there was early (proximal aortic band) versus late (distal aortic band) systolic wave reflection in the aorta. They found that while both forms of wave reflection stimulated greater left ventricular mass than a control rat, the early systolic load was better tolerated, with less overall left ventricular mass increase compared with the late systolic load. This research suggested that late systolic loading of the left ventricle would be a significant stimulus in the development of left ventricular hypertrophy and ultimately left ventricular failure.[11]

Based on such findings, our group performed two analyses of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort looking specifically at the role of increased wave reflection and the likelihood of heart failure in a population initially free of cardiovascular disease. MESA is a federally funded longitudinal cohort study that enrolled 6,814 men and women of African-American, Caucasian, Hispanic, or Chinese descent between the years 2000 and 2002.[12] MESA participants were free of known cardiovascular disease at the time of enrollment.

In the first evaluation, we used radial waveforms obtained in the sitting position during a MESA visit in 5,960 participants free of heart failure at enrollment.[13] The waveform depicted in Figure 2 was obtained from the stored information in the HDI Pulse Wave CR-2000 profiler device (Hypertension Diagnostics, Inc., Eagan, MN). Radial waveforms were submitted to a generalized transfer function,[14] and a central pressure waveform was derived as shown in Figure 2 on the right side. From the central waveform, first and second peaks (labeled as P1 and P2 in Figure 2) were identified using a published imputation technique,[15] and an augmentation index was calculated. Next, a physiologic flow waveform was derived with the aid of Matlab,[16] which allowed separation into

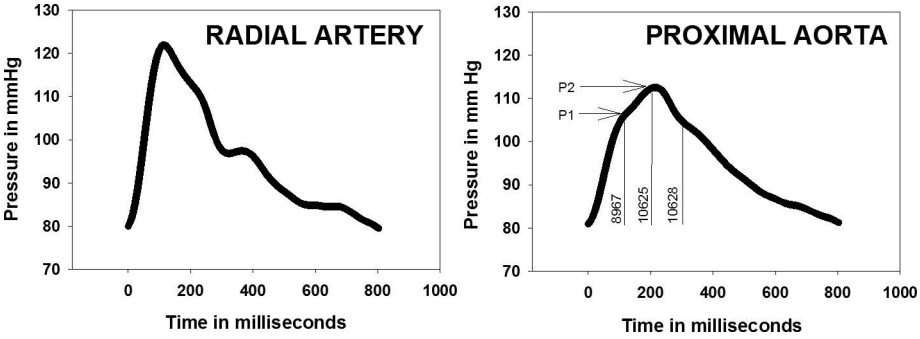

Figure 2. Left panel shows a radial artery pressure waveform. Right panel shows the proximal aortic waveform estimated from the radial waveform. The systolic portion of the central waveform was divided into systolic time integrals by thirds (each third is about 100 ms), and the area under the curve of each systolic time integral was computed in units of ms/mm Hg and shown as integers within each integral. The integrated area of the last third of systole (10628) divided by the first two-thirds (sum is 19592) yielded a value of 0.54.

forward- and backward-traveling pressure waves. We then divided the backward wave amplitude by the forward wave amplitude and multiplied it by 100 to calculate the reflection magnitude (RM). The average RM in MESA was 84. After a median follow-up of 7.6 years, there were 104 heart failure events in the MESA participants. Comparing RM to augmentation index, we observed that RM was a strong and significant predictor of heart failure, even when we adjusted for age, gender, cholesterols, smoking, blood pressure, diabetes, height and weight, medications, heart rate, and kidney function. Hypertensive participants with high RM had the highest likelihood of incident heart failure while normotensives with low RM had the lowest incidence of heart failure. Our novel observation was that hypertensives with a low RM and normotensives with a high RM had very similar heart failure occurrences. The accompanying editorial by Sanjiv Shah pointed out that RM could represent a novel form of stage B heart failure.[17]

Next, and apropos of the Kobayashi study,[11] we again used radial waveforms to generate the central aortic systolic pressure profile and then divided the central waveforms in the MESA participants into thirds (Figure 2).[18] We computed the area under the curve during systole (pressure versus time) for each of the three systolic segments in each participant (a standard Systolic Pressure Time Integral, or SPTI). We then computed the area under the curve of late systolic (third tertile) divided by the area under the curve of the first two tertiles, thereby deriving a $Late_{SPTI}$/$Early_{SPTI}$ ratio. The median value for the L_{SPTI}/E_{SPTI} ratio in the MESA cohort was 59%. With a longer follow-up in the MESA cohort (8.5 years at this point), there were 135 heart failure events. We observed that for each one standard deviation (S.D.) in the L_{SPTI}/E_{SPTI} value (one S.D. was 2.8%), there was an associated hazard ratio of 1.82 (95% CI 1.45- 2.28) for the occurrence of heart failure in the follow-up period. The editorial by Naomi Hamburg accompanying this finding speculated that late systolic loading may be an early warning signal for future heart failure.[19]

What Else do we Learn from Examining Central Pressure Profiles?

Pulse Pressure

Most of the excursion (pulse pressure) in the central waveform can be predicted from the radial or brachial pulse pressure. In general, about 80% to 85% of the pulse pressure will be evident once the brachial is known.[20] That said, there is some overlap so that the range of pulse pressure amplification (the brachial pulse pressure divided by the central pulse pressure) varies from < 1.1 to as high as 1.6 or more in some people. Greater degrees of pulse pressure amplification are thought to reflect healthier vessels. In the Strong Heart Study of Native Americans, central pulse pressures were estimated (in quartiles) from calibrated radial pressure tonometry by Mary Roman and colleagues[21] and compared with brachial pulse pressure quartiles. Roman noted that about half of the subsequent cardiovascular events occurred in the highest central pulse pressure quartile (> 50 mm Hg). The highest brachial pulse pressure quartile also had the greatest number of events, but the strength of the relationship between outcomes and pulse pressure was greater with the central measurements compared with the brachial measurements.

Augmentation Index

The augmentation index is determined by dividing the pressure increment between P2 and P1 in Figure 2 (right panel) by the central pulse pressure. In Figure 2, it would be 4 mm Hg/33 mm Hg = 12(%). The index is unitless and generally expressed as a percent. The augmentation index is a composite, or hybrid, finding that takes into account the pattern of left ventricular ejection, the velocity of pulse wave travel, the duration of systole, and the reflected wave magnitude. In the other meta-analysis of Vlachopoulos,[22] each 10% increase in the central augmentation index was associated with a 30% to 40% increase in cardiovascular outcomes and all-cause mortality.

Central Pressure Profiles and Interventions

The Conduit Arterial Function Evaluation (CAFÉ) was an early intervention trial that incorporated central pressure measurements into a substudy consisting of about 10% of the enrolled Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).[7,23] CAFÉ compared a regimen of calcium channel blockade (CCB) with angiotensin-converting enzyme inhibition (ACE-I) against a regimen of beta-blocker (BB) and diuretic over 4 years. Measurements of central pressures were not available at the time of randomization, but from the first annual visit onwards there was a 4 mm Hg lower central systolic pressure in the CCB/ACE-I arm compared with the BB/diuretic arm. At the same time, there was less than a 1 mm Hg systolic pressure difference in the brachial artery between the two intervention arms. These central systolic pressure changes were associated with a lower occurrence of cardiovascular events and kidney function impairment in CAFÉ.

Similarly, the Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study (REASON) compared a low-dose combination of the ACE-I perindopril with indapamide against the beta-blocker atenolol using the outcome of central (carotid artery) pressure changes.[24] The investigators noted similar declines in brachial diastolic blood pressure on the two regimens, but there was a greater brachial systolic pressure reduction with the ACE-I/indapamide combination as well as a greater decline in carotid artery systolic pressure. The same trial also examined changes in left ventricular mass and found that reductions in mass were about 3-fold larger in the ACE-I/indapamide group; this difference persisted even after controlling for differences in brachial systolic blood pressure.

In the clinic, the BP GUIDE study[25] used office-based assessments of central BP in managing hypertensive patients and was able to demonstrate a cost savings (by using less medication) without loss of evidence of adequate BP control as assessed by left ventricular mass, aortic stiffness, and the patient's reported quality of life.

Finally, the multiple-agent EXPLOR study compared 193 hypertensive subjects randomized to amlodipine combined with valsartan with 200 hypertensive subjects randomized to amlodipine combined with atenolol. As covered above, in the CAFÉ trial atenolol fared less well with respect to central pressure reduction compared to amlodipine. In the EXPLOR study, the goal was to determine if an angiotensin receptor blocker would retain better central pressure reduction compared with a beta-blocker when both classes of drug were combined with amlodipine. Despite similar changes in brachial blood pressure, the central systolic pressure declined more in the amlodipine/valsartan group (14 mm Hg) compared with the decline in the amlodipine/atenolol group (8 mm Hg). Interestingly, the pulse wave velocity decreased by the same amount (about 1 meter/second) in both intervention groups, again supporting the finding that the central pressure profile is only partly dependent on arterial stiffness, and that the magnitude of wave reflection, heart rate, and left ventricular ejection patterns also play a role.

Summary

The ability to noninvasively estimate pulse characteristics with reasonable accuracy over the past four decades has generated a resurgence of interest in the topic. The central pulse contour in particular represents a significant portion of the load experienced by the left ventricle with each heartbeat and appears useful in understanding why some patients with similar brachial blood pressure reduction may not experience as much target organ preservation. In particular, heart failure and left ventricular hypertrophy represent reasonable targets for intervention trials, which are the next logical steps to improve upon the clinical value of this novel yet ancient measure.

Conflict of Interest Disclosure: Dr. Townsend reports grants from the NIH and Fukuda Denshi and is a consultant to Janssen Pharmaceutica , Merck & Co., GlaxoSmithKline, and Medtronic, Inc. Dr. Townsend also receives royalties from UpToDate.

Keywords: renal denervation, sympathetic nervous system, resistant hypertension, blood pressure

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