Mini-Review

Vascular Stiffness: Its Measurement and Significance for Epidemiologic and Outcome Studies

Stephanie S. DeLoach and Raymond R. Townsend

Renal Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Arterial stiffness is recognized increasingly as an important component in the determination of cardiovascular risk, particularly in chronic kidney disease and ESRD populations. Although the technique has been around for nearly 100 yr, in the past 20 to 25 yr, pragmatic noninvasive approaches have allowed the incorporation of arterial stiffness measurements, usually in the form of aortic pulse wave velocity (PWV), into clinical assessment of patients. In populations with high cardiovascular risk, especially those with ESRD, aortic PWV measurements provide predictive utility independent of the standard brachial arterial BP measurements. This review briefly discusses the history of vascular dynamics, the determinants of PWV, and some of the available technologies in current use and concludes with a section on the relevance of arterial stiffness measurements in populations of particular interest to nephrologists.

Cardiovascular disease (CVD) is the leading cause of mortality for patients with kidney disease (1). Overrepresentation of traditional risk factors, such as hypertension, diabetes, and hyperlipidemia, in this group accounts for some of the increased morbidity; however, mortality rates exceed those expected after controlling for the aforementioned risk factors (2). This suggests that there are unique aspects of kidney disease that lead to an excess burden of CVD. Potential mediators of CVD that are unique to kidney disease include disordered bone mineral metabolism and vascular calcification. Recently, disordered bone mineral metabolism was linked to vascular stiffness (3,4). Vascular stiffness increases left ventricular afterload and decreases coronary perfusion, leading to CVD. Increased vascular stiffness, as measured by pulse wave velocity (PWV), is associated with increased cardiovascular and all-cause mortality in dialysis patients (5). Furthermore, dialysis patients who have a decrease in PWV in response to BP lowering have lower mortality rates compared with those who do not have a decrease in PWV (6) (more on this later); therefore, the study of vascular stiffness has the ability to give us additional information about CVD risk in chronic kidney disease (CKD), beyond traditional risk factors. Early recognition and modification of vascular stiffness may enable us to reduce CVD events in this population.

Interest in the human pulse dates back to ancient times, when Egyptian writings described the link between the arterial pulse and heart function (7). It was not until the 17th century that William Harvey was able to prove that the arterial pulse was the result of cardiac systole as detailed in his published work "An Anatomical Essay on the Movement of the Heart and Blood in Animals" (8). After that assertion, physicians and scientists sought to create models of vessel mechanics and devices that could capture the pulsatile excursion. The earliest endeavors to trace and record the arterial pulse took place during the 19th century (9). Ettiene Marey was the first to use a sphygmograph to record the arterial pulse in humans. Frederick Mahomed further described the relationship between the radial pulse and arterial pressure. His interpretation of radial artery waveforms using merely a sphygmograph enabled him to differentiate normotensive patients from those with essential and renovascular hypertension, before the availability of a cuff sphygmomanometer. Also in this century, Moens described the relationship between arterial elasticity and PWV. Clinical application of arterial elasticity and PWV expanded during the early 20th century. This was eclipsed by Otto Frank's development of the mercury column sphygmomanometer, which also emerged during this time period (10). The development of easy-to-use manometers in contrast to the complex calculations required for PWV led to the displacement of pulse waveform analysis in clinical practice for some time. During the later half of the century, the observation was made that with equivalent levels of BP control, some individuals went on to develop CVD and target organ damage and others did not. This led to the recognition that vascular mechanics, characteristic of the pulse contour and arterial stiffness, may also play a role in progression of CVD. These observations and the development of Doppler ultrasound, pressure transducers and applanation tonometry prompted a re-emergence of clinical applications for arterial stiffness measurements, particularly PWV.

The palpable peripheral pulse results from a pressure wave that follows left ventricular contraction during systole. This pressure wave is a composite of left ventricular contraction, properties of the blood (*e.g.*, viscosity), and characteristics of the arterial tree. The pressure wave is propagated forward during systole until it reaches branch points, areas of turbulent or

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stagnant flow, changes in lumen diameter, and other aspects in the arterial tree, at which point the wave is reflected back. The final pressure wave in the vessel is the sum of the forward and reflected waves, as shown in Figure 1. This reflected wave is important because, physiologically, it should return in bulk to central circulation during early diastole and augment coronary blood flow. This is the case in individuals with elastic arteries. In the case of individuals with stiff, noncompliant arteries, the bulk of this reflected wave returns to central circulation sooner, during late systole, thereby increasing cardiac workload and decreasing the pressure support for coronary perfusion, as seen in Figure 1 (bottom).

The importance of vascular disease in patients with CKD cannot be overemphasized. Patients with CKD, particularly when diabetes is present, are five- to 10-fold more likely to die than to experience ESRD when they reach Medicare eligibility (11). Moreover, in patients with CKD, heart disease is twice as common and advances at twice the rate compared with those without CKD. In patients with CKD, the high prevalence of diabetes with its tendency to build up collagen in vessel walls from glycation end-product accumulation, impairing normal matrix turnover (12), the substantial incidence of hypertension (regardless of whether diabetes is present) (13), and the frequent occurrence of aortic vascular calcification (14) contribute through vascular stiffening to this high rate of CVD.

In the rest of this review, we cover some basic determinants of PWV, provide an overview of available office-based measurement technologies, and conclude with coverage of arterial stiffness measures in CKD/ESRD. The field has expanded greatly in the past 20 yr, and in this review we focus on stiffness measures particularly but not exclusively in CKD/ESRD populations.

Aortic PWV and Its Determinants

The PWV can be viewed mathematically or pragmatically. From a mathematics sense, a formula called the Moens-Korteweg equation that relates PWV to a function of elastic modulus, viscosity, and vessel diameter in this manner has been derived:

$$V = \sqrt{(Eh/2 \mathrm{p} R}$$

where V is wave speed, E is Young's elastic modulus in the circumferential direction (this modulus is a ratio of stress/strain, i.e., a way to represent the effects of force [stress] on shape [strain]), h is the wall thickness, ρ is the density of the fluid, and R is the radius of the vessel (15).

From a pragmatic sense, the velocity is simply how fast the pulse wave travels a specified distance of the vascular bed. This has been the clinical approach to measuring PWV in recent times. The steps involved in the actual technique are described later in this review.

Genes

Aortic PWV is a heritable trait, according to Framingham data (16). Several genetic polymorphisms have been reported to influence PWV, including those for the AT_1 receptor (17), fibril-
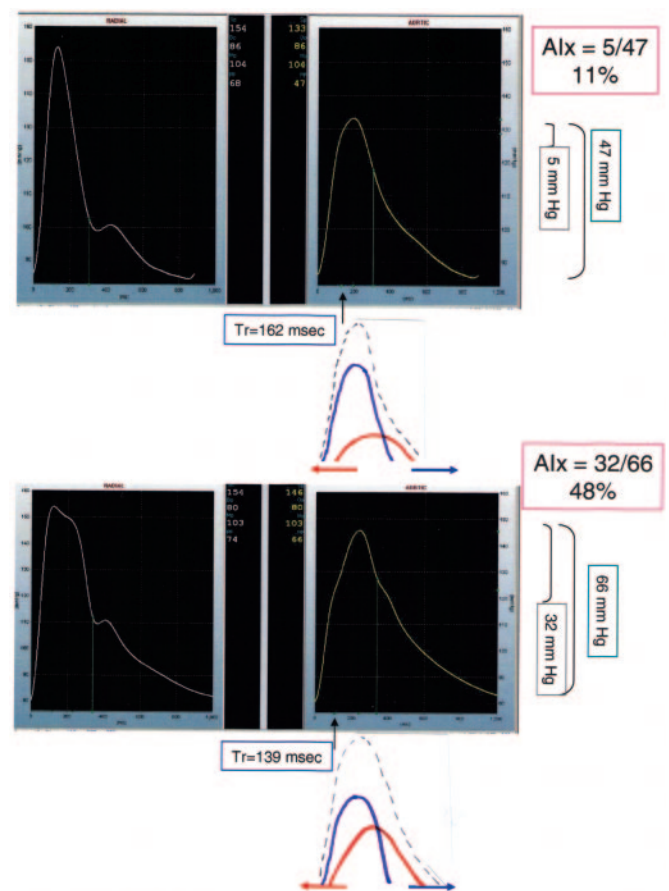
Figure 1. Pulse wave analyses performed on two 68-yr-old men who were enrolled in the Chronic Renal Insufficiency Cohort Study (60). Both had brachial systolic BP (SBP) of 154 mmHg. In both panels, the left side of the figure depicts a radial artery waveform acquired using the SphygmoCor system (see text). The right side of each figure shows the aortic pressure profile. Despite similar brachial (labeled "RA-DIAL") SBP, the central aortic systolic pressure in the top panel is 133 mmHg compared with a value of 146 mmHg in the bottom panel. The black vertical arrows mark the time to reflection (Tr), which detects the leading edge of the backward-traveling wave forms (depicted in red below each of the two aortic pressure profiles). In the bottom panel, the Tr is 139 ms (green dot just past tip of black arrow), shorter than the 162 ms recorded in the top panel and consistent with greater vessel stiffness as demonstrated by a 20% higher aortic pulse wave velocity (PWV; data not shown) recorded in the patient depicted in the bottom panel. Beneath each aortic pressure profile on the right are schematics of forward-traveling (blue) and backward-traveling (red) waves. The dotted line represents their summation and is similar to the aortic profile directly above it. At the bottom of each panel on the aortic side is a middle green dot, which depicts the peak pressure in the aorta. This peak pressure minus the diastolic yields the aortic pulse pressure: 47 mmHg in the top panel and 66 mmHg in the bottom panel. The difference in aortic pressure at the Tr subtracted from that at peak generates the augmented pressure from the red backward-traveling wave. When this pressure augmentation is divided by the pulse pressure, it yields the augmentation index (AIx): 11% in the top panel compared with 48% in the bottom panel.

lin-1 (18), metalloproteinases (19), and the endothelin pathway (20).

Vessel Wall Proteins

Stiffness is also related to the relative amounts of elastin and collagen in the vessel wall. The more proximal parts of the aorta, which have slower velocities, contain relatively greater proportions of elastin compared with collagen. As one proceeds distally, this ratio changes (21). Collagen also accumulates (relative to elastin) in the aorta with age and comorbidities such as hypertension, diabetes, and cigarette use. Excessive intramural build-up of other proteins, such as integrins, fibronectin, and desmin, also increase vascular stiffness (22).

Age

Age has one of the clearest effects on aortic PWV. Even in otherwise healthy individuals, aging results in an alteration of elastic wall components that generates an increase in stiffness (23). Years of cyclic pulsatile stress lead to fragmentation of vascular elastin elements and accumulation of load-bearing collagen with a loss of stretch and increase in stiffness reflected by a steadily increasing systolic pressure (24).

Systolic and Pulse Pressures

Systolic BP (SBP) and pulse pressure abet age-related changes in vessel stiffness by enhancing the magnitude of the pulsatile component of the stress and strain placed on the vessel with each heartbeat (25). In addition, the level of BP creates an initial "loading" condition that regulates pressure wave conductance in the aorta. Increasing the BP in an individual will increase the PWV (26).

Calcification

Vascular calcification plays a substantial role in aortic stiffness, especially in patients who have reached ESRD (27). Low bone turnover rates coupled with vitamin D and calcium salt therapies may be a "perfect storm" setting for deposition of calcium in the aorta (4). Aortic calcium loads as evidenced on lateral lumbar x-rays are directly related to aortic PWV (28).

Sodium Intake

Although salt intake may be naturally linked to an increase in SBP and thus stiffness, there are clear instances in models of hypertension in which aortic stiffness results from increased salt intake independent of BP changes (29).

Kidney Failure

Some of the most impressive data on cardiovascular outcomes in patients with stiff aortas have come from the ESRD population. Although it is clear that aortic PWV is increased in renal failure, specific mechanisms related to kidney failure apart from those covered already are not apparent yet but are an intensely active area of investigation.

Diabetes

Diabetes adds to the aortic PWV independent of other comorbidities or pathophysiologies, such SBP, kidney failure, and

aging (30,31). Diabetes has long been thought a model of accelerated aging (32), and the build-up of inelastic matrix materials similar to that of aging in vessel wall and their subsequent glycation is a principal mechanism of the effects of diabetes on aortic PWV (33).

Office-Based Devices that Measure Arterial Stiffness

A number of devices to measure arterial stiffness are commercially available. Noninvasive measurement of arterial stiffness usually falls into one of three categories:

- Devices that measure PWV
- Devices that measure arterial distensibility
- Devices that provide assessments of peripheral arterial pressure waveforms (*e.g.*, augmentation index [AIx])

Most of these devices derive their measure of arterial stiffness from peripherally acquired waveforms using tonometry, a validated technique (34). The technique of tonometry is fairly simple to learn and has good inter- and intraoperator reproducibility (35). The gold standard of arterial stiffness measurements is aortic PWV. For PWV measurement, velocity is expressed as change in distance over change in time ($V = \Delta D/\Delta T$). Distance is measured at two sites along a single vessel or at two separate sites in the arterial tree. Time is determined two ways. One way is to use an event in the pulse tracing such as the tip of the QRS complex as a timing "anchor" and record the pulse onset in one site at a time, deriving the "time elapsed" as

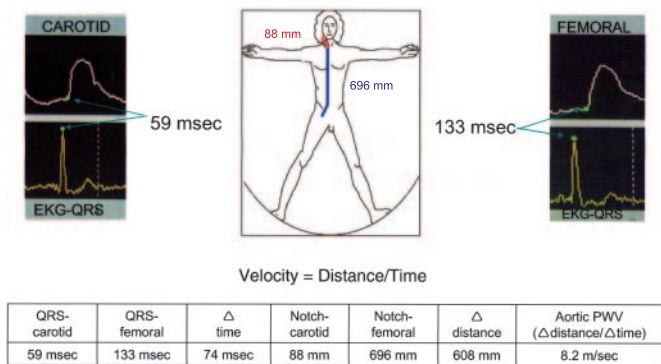| QRS-carotid	QRS-femoral	Δ time	Notch-carotid	Notch-femoral	Δ distance	Aortic PWV (Δdistance/Δtime)
59 msec	133 msec	74 msec	88 mm	696 mm	608 mm	8.2 m/sec

Figure 2. Elements necessary to measure PWV if done by tonometry coupled with electrocardiography (EKG). Distance from sternal notch to carotid pulse site (red) and distance from sternal notch to umbilicus and then to groin (in blue) are measured as shown. The probe captures the wave form at the carotid and femoral sites, and the time elapsed between the tip of the QRS complex and the onset, or "foot," of the pulse wave is calculated. Generally, 10 s worth of data are captured, yielding six to 11 beats, which are averaged for the elapsed time at the carotid and femoral sites. The distance divided by time generates the velocity. Because the distances are in millimeters and the times are in milliseconds, the "milli" cancels out, leaving units of m/s.

Table 1.   Commercial devices that measure arterial stiffness[a]

Device	Manufacturer	Measure	Pros	Cons
SphygmoCor	AtCor Medical (www.atcormedical.com)	PWV *via* applanation tonometry	Measures central PWV and AIx	Limited by technical difficulty in obtaining measurements
Colin VP-1000	Omron Healthcare (www.omronhealthcare.com)	PWV, AIx, ABI	Measures central AIx	Does not measure central PWV
HEM9000AI	Omron Healthcare (www.omronhealthcare.com)	Radial AIx	Measure of peripheral arterial stiffness	No measurement of central AIx Peripheral waveform analysis cannot reliably predict central AIx or pulse pressure
HDI/PulseWave CR-2000 and CVProfilor DO-2020	Hypertension Diagnostics (www.hdi-pulsewave.com)	Large- and small-vessel elasticity (compliance)	Distinguishes stiffness of small and large peripheral arteries	Measures compliance expressed as elasticity, which is limited by variations in compliance throughout the arterial tree largely as a result of change in vessel size C2 calculations hampered by variations in SVR and reflected waves No measurement of central SBP
DynaPulse 2000	Pulse Metric (www.pulsemetric.com)	Brachial artery distensibility	Measures peripheral artery distensibility, which may be superior to compliance	Brachial artery distensibility may not be reflective of central or large-vessel elasticity Estimates only central BP values
Complior	Artech Medical (www.artech-medical.com)	PWV	Obtains central PWV, taking simultaneous measures at carotid and femoral sites	Digitized waveforms create difficulty in discerning "foot" (arrival time) of the wave
PulseTrace PWV and PCA 2	Micro Medical (www.micromedical.co.uk)	PWV *via* photoplethysmography	Measures central PWV	SI and RI lack reproducibility, outcome data

[a]ABI, ankle-brachial index; AIx, augmentation index; PWV, pulse wave velocity; RI, reflection index; SBP, systolic BP; SI, stiffness index; SVR, systemic vascular resistance.

shown in Figure 2. The other way is to record the pulse wave at two different sites associated with the same heartbeat so that the measurement is simultaneously done for each pulse. PWV by photoplethysmography has been validated by correlation with intra-arterial sensing techniques (36). A comparison of available devices for measurement of arterial stiffness is discussed next. Table 1 lists some currently available devices that measure arterial stiffness.

The SphygmoCor device, produced by AtCor Medical (West Ryde, Australia), uses peripheral waveforms (usually from the carotid and femoral arteries) to measure PWV. Figure 3 shows a typical unit and its approximate size. Applanation tonometry using a Millar tonometer is performed simultaneously with an electrocardiogram (ECG). In this manner, aortic PWV is measured (see Figure 2). This device can also measure aortic AIx using radial artery–based pulse wave analysis to derive the central aortic BP profile (see Figure 1) through the use of a validated transfer algorithm (37). AIx, which results from the summation of the forward pressure wave and reflected wave coming from the periphery, is also a measure of arterial stiffness as shown in Figure 1. The AIx correlates with mean arterial pressure and inversely relates to heart rate and body height. AtCorMedical's SphygmoCor is attached to a PC or laptop and requires its own power source. This device has the advantage of having been used in large longitudinal observation studies in which PWV was demonstrated to correlate with cardiovascular events in ESRD (5,38). Importantly, in ESRD, AIx is predictive of mortality even in the setting of normal PWV (38). We will not say much more about AIx in this review because vascular stiffness is only one determinant of the AIx (the others include

the magnitude of the reflected wave and characteristics of the ventricular ejection profile). The reader is referred to references (39–41) for recent reviews of AIx.

The Colin VP-1000, produced by Omron Healthcare (Bannockburn, IL), also measures PWV. This device uses four BP cuffs (at both brachial arteries and ankles) and ECG, allowing for simultaneous PWV and ankle-brachial index measurements. The PWV as measured with this device uses muscular

Figure 3. SphygmoCor device. Most stiffness-measuring units are portable and lightweight.

arteries, so central or aortic PWV is only inferred. A pressure transducer can assess carotid pressure waveform to derive an AIx. The unit is self-contained and does not require attachment to a PC or laptop; however, the quality of waveforms compared with those obtained using other devices is less, and the published experience with the VP-1000 is limited. The VP-1000 was formerly produced by Colin Medical. After acquisition by Omron Healthcare, this technology has been replaced somewhat by their HEM-9000AI, discussed next.

Omron Healthcare also produces the HEM9000AI, which became available for use in the United States in 2006. It uses a radial artery waveform for pulse wave analysis to derive a peripheral AIx. A multiarray sensor obtains semiautomatic radial tonometry measurements. This device also has a BP cuff for simultaneous measurement of brachial BP. The radial AIx is graphed and compared with normal values according to demographic group. This device does not measure central pressures. Omron's HEM9000AI is also self-contained. It comes complete with a keyboard and printer.

Hypertension Diagnostics (Eagan, MN) produces the DO-2020 and CR-2000 for arterial stiffness measurement. The HDI/PulseWave CR-2000, currently used solely for research purposes, and the CVProfilor DO-2020, used for clinical purposes, are noninvasive devices that use BP waveform analysis to determine arterial elasticity. Specifically, this device measures large, or capacitive, compliance (C1), and small, or oscillatory, compliance (C2) artery elasticity indexes. Compliance describes a change in volume for a given pressure change. This device and its measurements are based on a modified Windkessel model (42) in which arterial circulation is related to two capacitance circuits. The diastolic component of the pressure waveform is used to derive compliance. The HDI/PulseWave uses a standard BP cuff and automated tonometer to obtain radial and brachial arterial measurements using an oscillometric technique. The pressures recorded by the HDI/PulseWave have been validated by comparison with mercury sphygmomanometry (43). The HDI/PulseWave has been used to demonstrate an inverse relationship between large- and small-vessel elasticity and BP (44). The HDI/PulseWave CR-2000 can also estimate other cardiac parameters, such as stroke volume, cardiac output, and cardiac index, and measures systemic vascular resistance. These devices do not produce information about central pressures. Other criticisms of this device are regarding the exact nature of what the C2 measurement reflects (*i.e.*, difficult to separate from systemic vascular resistance) (45) and the degree of variability in cardiac output estimate.

Pulse Metric (San Diego, CA) produces the DynaPulse 2000 device. This device measures arterial stiffness through characterization of peripheral arterial (usually the brachial artery) distensibility. Arterial distensibility, expressed as compliance (volume/pressure, ml/mmHg), is derived from that peripheral arterial waveform. The DynaPulse 2000 uses an oscillometric technique. Specifically, a standard BP cuff is applied. Sensors within the cuff detect the waveform of the arterial pulse. This technique allows for estimation of central BP; brachial artery distensibility; and cardiac parameters, such as cardiac output, stroke volume, and systemic vascular resistance. Although central BP is estimated, elasticity is not measured. The measurements are submitted online to a central database (DynaPulse Analysis Center) for analysis and reporting. Pulse Metric's device has the advantage of validation of its BP and compliance measurements by correlation with invasive catheter measurements in the aorta (46). The DynaPulse 2000 has been used in clinical research to demonstrate the relationship between cardiovascular risk factors and coronary artery calcification (47,48).

The Complior is produced by Artech Medical (Pantin, France). This device uses four (carotid, radial, femoral, and distal) piezoelectric pressure sensors for simultaneous arterial waveform measurement. The sensors allow for measurement of PWV at various arterial segments: Carotid-femoral (aortic stiffness), carotid-radial (upper extremity arterial stiffness), brachial-radial (forearm arterial stiffness), and femorotibial (lower extremity arterial stiffness). In addition, estimated central aortic pulse pressure and an arterial stiffness index are measured. The small device connects to a computer and uses a USB port for its power source. Studies using this device to measure PWV have also demonstrated its correlation with cardiovascular risk factors (49).

Micro Medical produces two devices, the PulseTrace PCA 2 and PulseTracePWV, for measurement of arterial stiffness. The PCA 2 uses a photoplethysmography technique to obtain digital volume pulse from a finger probe. The PCA 2 device relates digital volume pulse to peripheral pressure waves, such as those obtained by radial applanation tonometry, using a transfer algorithm (50). Experience with digital pulse volume is limited, and this technique has not been correlated with central arterial stiffness. The PulseTrace PWV measures arterial waveforms at two sites along the arterial tree (carotid and femoral) using a Doppler probe and with simultaneous ECG. Measurements are reported as a stiffness index and a reflection index. The stiffness index is a measure of PWV in large arteries. It is a measure of the timing of the diastolic relative to the systolic component of PWV in the large arteries (height divided by time between systolic and diastolic peaks). The stiffness index has been shown to correlate well with central PWV (51). Reflection index is a measure of small artery stiffness. The diastolic peak is expressed as a percentage of the systolic peak and correlates with pulse wave reflection and tone of small arteries. The unit is self-contained and does not require an external PC or laptop. A disadvantage of these devices is the inferior quality of waveform obtained from the finger probe compared with radial applanation tonometry.

In selecting a device, the manner in which arterial stiffness is measured should be considered. Other issues to consider are time and space available to conduct the procedure, any required training, the technical expertise of personnel conducting the tests, and the cost of the device. For example, applanation tonometry is an easily learned technique and can be done quickly in an outpatient setting. In contrast, ultrasonography- or magnetic resonance imaging–based approaches (not reviewed here but covered in reference [35]) to measuring PWV are more costly (equipment-wise) and time-consuming and require more extensive training for proficiency.

Clinical Relevance of PWV

Here we review some representative studies that help to develop a frame of reference about what stiffness measures may add to our understanding of disease pathogenesis and the treatment of patients with CKD.

We begin this last segment by posing three questions:

1. Why aortic PWV?
2. Does aortic PWV add independently to standard measurements of BP?
3. Why is PWV able to predict cardiovascular outcomes independent of standard CV risk factors?

Aortic PWV

PWV can be calculated in any segment of the circulation as long as the distance and the elapsed time that the wave travels that distance can be measured. There are two reasons that aortic PWV is the favored measurement. The first is anatomic, in that the vessels whose organs are particular targets of hypertension, irrespective of the presence of CKD, all are connected to the aorta. These include the carotid, the coronary, and the renal vessels. It is clear that the systolic pressure varies in different arterial beds within the same person depending on the interaction of the forward and backward traveling waves, and part of this discrepancy is related to vessel stiffness. Thus, although knowing the standard brachial pressure gives a clue about the aortic stiffness and knowledge of the pulse pressure refines the clue somewhat because it sharpens the estimate by incorporating the diastolic pressure, a direct measurement of stiffness such as PWV provides the best estimate of aortic stiffness (52,53). The second reason is that the aortic stiffness is more predictive of CVD deaths compared with PWV measured in the brachial or femoral circuits in ESRD. In 305 hemodialysis patients, the aortic, brachial, and femorotibial PWV were determined initially, and the patients were followed longitudinally for an average of 6 yr (54). The cardiovascular survival results are shown in Figure 4. These results support the idea that the aorta, an elastic capacitance vessel whose PWV is usually lower than the velocity in muscular conduit arteries such as the brachial or the femorotibial, shows much more change with aging and comorbidities. A typical aortic PWV in a healthy 20-yr-old is approximately 4.5 m/s. A typical brachial PWV in the same person would be 9 m/s. When that person reaches 70 yr and remains in good health, the aortic velocity will have risen to approximately 10 to 11 m/s (2.5-fold increase), whereas the brachial velocity will be approximately 11 to 12 m/s (1.3-fold increase) (23). The change in PWV in the aorta from aging and various comorbidities is greater than the change in PWV in muscular artery circuits such as the brachial or the femorotibial. The robustness of PWV measures in the aorta makes it the most informative vessel for cardiovascular outcomes prediction.

PWV: Independent Prediction of Cardiovascular End Points

Several lines of evidence now support an independent predictive ability of PWV for cardiovascular outcomes. In the Health, Aging and Body Composition (Health ABC) Study, approximately 3000 patients who were aged 70 to 79 yr were enrolled
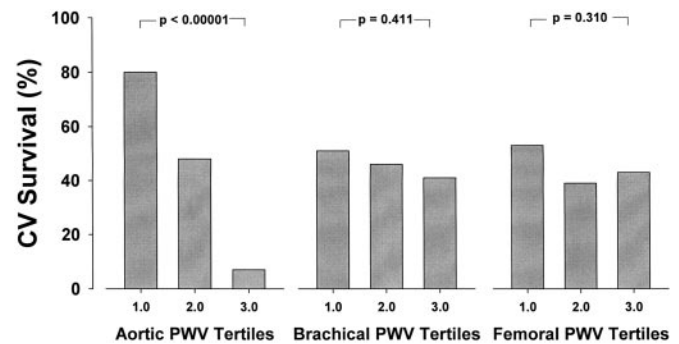

Figure 4. Longitudinal follow up of more than 300 dialysis patients who had PWV measurements performed in aorta, brachial/radial, and femoral/tibial vascular beds. Primary outcome was cardiovascular survival. Average follow-up was 70 mo. Patients were divided into tertiles by the velocities obtained in each bed. The aortic PWV tertiles had a very clear relationship to survival, whereas division of patients by brachial or femoral PWV tertiles was not significantly predictive of survival. This figure is adapted from reference (54).

between 1997 and 1999 in Pittsburgh and Memphis and followed longitudinally. Aortic PWV showed a clear association with cardiovascular events at each quartile of increasing velocity independent of age, gender, SBP, race, or known previous CVD (55).

In populations that are at inherently less overall cardiovascular risk as a result of a younger age, aortic PWV has again been shown to have independent prediction potential. A study in Paris of approximately 2000 patients who had hypertension and were on average 50 yr of age at enrollment showed a strong relationship of aortic PWV in increments of 5 m/s with cardiovascular mortality independent of previous CVD, age, and the presence of diabetes (52). Another French study of 1700 patients who had hypertension and were free of known CVD at enrollment showed that aortic PWV in increments of 4 m/s predicted fatal stroke independent of age and cigarette use (53). In the same study, neither pulse pressure nor SBP improved the fit of the statistical model over the effects of age.

A different population of approximately 400 patients with diabetes in the United Kingdom were studied with an 11-yr follow-up. In this population, 45% died during the follow-up period. Age and gender were significant independent predictors of death, and PWV increments of 1 m/s had a significant independent effect on mortality. In the Cox regression model, neither brachial SBP nor pulse pressure had independent prediction potential when PWV was used (56).

A prospective study of 150 dialysis patients who had hypertension illustrates the value of longitudinal changes in aortic PWV with time (6). Their BP was initially treated with target weight adjustment and additional angiotensin-converting enzyme inhibitor or calcium channel blocker therapy (randomly assigned) if still elevated. They were followed for a little more than 4 yr. Fifty-nine patients died during the follow-up period. The results are shown in Figure 5. The point made was that the aortic PWV in those who died during follow-up (Figure 5,
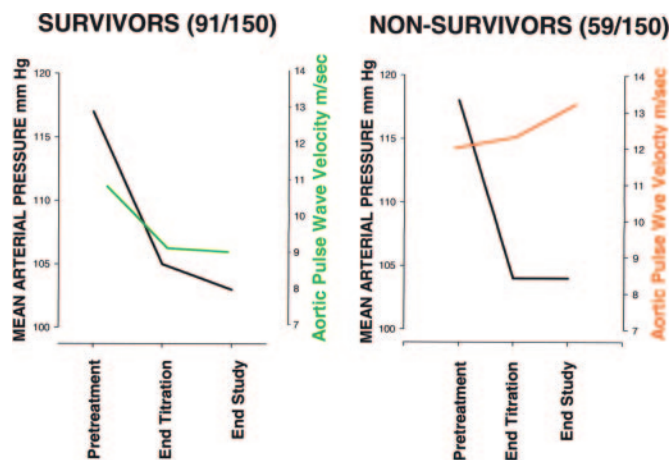
Figure 5. A total of 150 dialysis patients washed out of previous antihypertensive therapy (Pretreatment) and underwent periodic evaluation of aortic PWV (line indicating PWV is color coded to ordinate on right of each panel). See text for details of treatment. Primary outcome was survival. Those with faster aortic PWV that did not decline with antihypertensive treatment were more likely to die. This figure is adapted from reference (6).

right) began at a higher average value and rose, rather than fell, despite BP reduction, supporting the idea that the aortic PWV, not the BP *per se*, was indicative of death during the period of observation. An overview of 11 studies showing the independent predictive ability of aortic PWV is found in Table 4 of reference (35).

Why PWV Predicts Independent of Standard BP Measurements

To address why PWV predicts independent of standard BP measurements, keep in mind that what the left ventricle "sees" is the SBP in the aorta, not the brachial artery. The SBP in the aorta is determined in substantial part by the velocity of the returning wave (hence the stiffness aspect) as well as the magnitude (*i.e.*, the height in mmHg) of the reflected wave, how far away the average reflection sites are, and the ventricular ejection pattern. As increasing stiffness shifts the bulk effect of the returning wave from early diastole into late systole, the result is extra pressure on the left ventricle and a reduction in early diastolic pressure, as shown in Figure 1.

Next, it helps to think of arterial stiffness as an "intermediate" end point. We typically catalog and/or measure cardiovascular risk factors when evaluating an individual, but these represent static points. They fluctuate, and they may not provide a sense of "cumulative effect" other than perhaps years of diabetes or cigarette smoking. A measure of aortic stiffness, however, gauges the result of these risk factors on an intermediate target, the aorta itself. As such, it may be a better reflector of the cumulative effects and interactions of cardiovascular risk factors and comorbidities because it likely represents their translation into an intermediate phenotype (stiffness), as depicted in Figure 6.
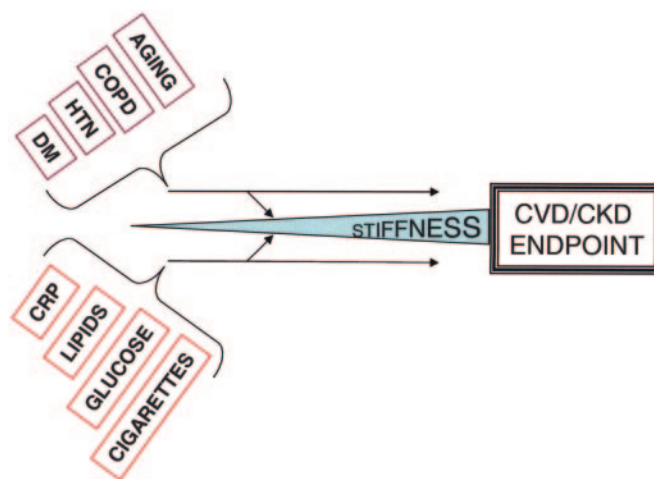

Figure 6. Authors' concept of aortic stiffness in relation to other cardiovascular risk factors. See text for details. Biomarkers in particular, although well established predictors of cardiac and renal end points, are static values and give no information on their cumulative effect until an end point such as a heart attack occurs. Aortic stiffness reflects the intermediate effects of biomarkers and comorbidities and may help to identify those who are at higher risk and perhaps warrant more aggressive management of their risk factors. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes; HTN, hypertension.

Conclusions

Increasing arterial stiffness is a major factor contributing to the rise in SBP with age. Because the pressure wave is amplified as it travels to the brachial artery, a standard BP may not fully reflect the central aortic pressure profile because of interindividual variation in aortic stiffness. Measurement of aortic PWV is the best available noninvasive measure of arterial stiffness and correlates well with subsequent risk for CVD. A number of studies have demonstrated its independent predictive utility for cardiovascular outcomes when compared with standard BP and other routine demographics. What remains in the field are studies of cardiovascular outcomes using PWV as a treatment end point, perhaps incorporating compounds such as alagebrium, which have more stiffness-reducing than antihypertensive effects (33). Other opportunities include manipulating divalent ion metabolism to reduce calcification (57), perhaps leveraging endocrine systems such as fetuin A that inhibit vascular calcification (58), and closer attention (*i.e.*, incorporating measures of central hemodynamics) to the central BP effects of antihypertensive medications, which all lower brachial BP but differ in their effects on central hemodynamics (59).

Acknowledgments

Disclosures

None.

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