AHA Scientific Statement

Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness

A Scientific Statement From the American Heart Association

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Much has been published in the past 20 years on the use of measurements of arterial stiffness in animal and human research studies. This summary statement was commissioned by the American Heart Association to address issues concerning the nomenclature, methodologies, utility, limitations, and gaps in knowledge in this rapidly evolving field. The following represents an executive version of the larger online-only Data Supplement and is intended to give the reader a sense of why arterial stiffness is important, how it is measured, the situations in which it has been useful, its limitations, and questions that remain to be addressed in this field. Throughout the document, pulse-wave velocity (PWV; measured in meters per second) and variations such as carotid-femoral PWV (cfPWV; measured in meters per second) are used. PWV without modification is used in the general sense of arterial stiffness. The addition of lowercase modifiers such as "cf" is used when speaking of specific segments of the arterial circulation.

The ability to measure arterial stiffness has been present for many years, but the measurement was invasive in the early times. The improvement in technologies to enable repeated, minimal-risk, reproducible measures of this aspect of circulatory physiology led to its incorporation into longitudinal cohort studies spanning a variety of clinical populations, including those at extreme cardiovascular risk (patients on dialysis), those with comorbidities such as diabetes mellitus (DM) and hypertension, healthy elders, and general populations.

In the ≈3 decades of clinical use of PWV measures in humans, we have learned much about the importance of this parameter. PWV has proven to have independent predictive utility when evaluated in conjunction with standard risk factors for death and cardiovascular disease (CVD). However, the field of arterial stiffness investigation, which has exploded over the past 20 years, has proliferated without logistical guidance for clinical and translational research investigators. This summary statement, commissioned by the American Heart Association Council on Hypertension, represents an effort to provide such guidance, drawing on the expertise of experienced clinical and basic science investigators in Europe, Australia, and the United States. Recommendations made in this statement are assumed to refer to the research aspect of arterial stiffness investigations, unless accompanied by language that emphasizes clinical use as well, and are based on the grid shown in Table 1.

Section 1. What Is Arterial Stiffness?

Recommendation

1.1. It is reasonable to measure arterial stiffness clinically by determining PWV (*Class IIa; Level of Evidence A*).[1]

Arterial stiffness is a concept that refers to the material properties of the arterial wall, which in turn has functional consequences for the artery because it affects the manner in which

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

pressure, blood flow, and arterial diameter change with each heartbeat. In addition to the passive mechanical properties of the load-bearing structures, arterial stiffness can be modulated by functional components related to cellular processes in which wall stiffness can be affected by endothelial function through modulation of smooth muscle tone or by alterations in the integrity of the extracellular matrix. As developed in this summary statement, stiffness is measured in different kinds of arteries (muscular, elastic) and in cross section, longitudinally along the vessel, or in both directions. Often, arterial stiffness is assessed as the velocity of pulse-wave travel in a defined segment such as the aorta. However, the research questions addressed by investigations of arterial stiffness are not restricted to this use, and stiffness has been measured in most named large arteries in humans.[2] Arterial stiffness is also estimated by measuring pressure or diameter in a vessel and applying 1 or several of the now extensive formulas to the data to derive a value that reflects this inherent property of all arteries.[3]

Surrogate Measures of Arterial Stiffness and What Is Not Technically Stiffness

Arterial stiffness is often determined by measuring the velocity of pulse-wave travel in a segment of vessel.[1] This is a valid measure, justified by equations such as the Moens-Korteweg and Bramwell Hill equations with which these measures agree.[3] Other methods to measure arterial stiffness include the

assessment of arterial compliance or distensibility or measures of characteristic impedance (relating pressure changes to flow changes). When arterial geometry (size and wall thickness) is known, it can be used to compute the arterial wall elastic modulus, a direct expression of the stiffness of the wall. Confusion arises when measures such as systolic pressure augmentation, which compares the first and second systolic peaks in the central aortic waveform and is sometimes reported as an augmentation index (AIx), are presented as "stiffness" parameters. Such measures are the result of several factors, including, but not limited to, arterial stiffness (described further in the Section 4).[4]

The Arterial Wall and Stiffness

Arterial stiffness refers to the material properties of the arterial wall, which in turn affect the manner in which pressure, blood flow, and arterial diameter change with each heartbeat. The pressure load of each heartbeat in large conduit arteries is borne mainly by the elastin and collagen components, with less contribution from smooth muscle in the muscular arteries. Because of the anatomic arrangement of the elastin and collagen fibers, elastin engages at low distention (hence at low pressure) and collagen at higher distention (and pressure).[5] The contribution of elastin and collagen to wall stiffness along the aorta varies as distance from the aortic valve increases to optimize the reservoir function of the aorta.

Arterial stiffness is a major determinant of vascular impedance. Impedance relates the change in arterial pressure to the change in blood flow. Flow is determined by the presence of a pressure gradient. The relationships between time, pressure, and flow are such that local wave velocity becomes a determinant of the instantaneous relationship between pressure and flow. For elastic conduits, wave velocity is related to the stiffness of the wall, so changes in stiffness will modulate the pressure/flow relationships. The need to buffer each stroke volume and to adapt to changes in flow requires an optimal balance in the elastic and inelastic elements in the wall. Disease, aging, and other exposures typically reduce the elastic component and promote the inelastic (collagen) component such that arterial stiffness generally increases with age in most people.

Changes in arterial stiffness fall into passive and active categories. Passive categories relate to arterial wall fiber elements that are stretched and recoil with each heartbeat and to heart rate (higher heart rates can be associated with increased arterial stiffness[6]). Active categories include endothelial function as it relates to nitric oxide and endothelin and vascular smooth muscle in which higher resting tone is associated with increased arterial stiffness.[7] Inflammation, oxidative stress, and turnover in the extracellular matrix of the vessel wall are additional active contributors to arterial stiffness.[8] In addition, sympathetic tone and genetic polymorphisms appear to regulate arterial stiffness in some vascular beds. The degree of the passive and active (functional) effects on wall stiffness depends on the type of artery: A greater degree of functional effects would be manifest in more muscular arteries (eg, carotid, iliac) compared with larger nonmuscular conduit arteries (eg, aorta).

Section 2: Devices Used to Measure PWV

Recommendations

2.1. Arterial stiffness should be determined noninvasively by measurement of cfPWV (*Class I; Level of Evidence A*).[9,10]

2.2. PWVs measured in other vascular segments such as ankle-brachial or the determination of the cardiac-ankle vascular stiffness index is useful in cardiovascular outcome predictions in Asian populations, but longitudinal studies in the United States and Europe by these methods are lacking (*Class I; Level of Evidence B*).[11,12]

2.3. Single-point estimates of PWV are not recommended because there is a lack of evidence of cardiovascular outcome prediction in longitudinal studies. Measurement of PWV in other arterial segments such as carotid-radial is not recommended because it does not predict outcomes (*Class III; Level of Evidence B*).[13]

Measurements of PWV are undertaken with several methodologies, some of which require sophisticated equipment (magnetic resonance imaging [MRI]) and software. These fall into 4 categories:

- Devices that use a probe or tonometer to record the pulse wave with a transducer
- Devices using cuffs placed around the limbs or the neck that record arrival of the pulse wave oscillometrically
- Ultrasonography approaches
- MRI-based approaches

Devices Using a Probe or a Tonometer to Measure PWV

A number of devices based on this technology are available and have been used extensively in published research. Tonometry-based techniques (eg, the SphygmoCor device, AtCor Medical, West Ryde, NSW, Australia) use a piezoelectric Millar tonometer that is placed at any 2 sites where a pulse is detectable. Only 1 tonometer is attached to the unit, so PWV measurements require 2 sequential 10- to 20-second readings, gated to the ECG, to be taken. The average transit time (TT) is then derived with the R wave of the ECG used as a reference point, and PWV is calculated from the inputted distance measurement. The SphygmoCor device has been used in the Anglo-Cardiff Collaborative Study of arterial stiffness[14] and the Chronic Renal Insufficiency Cohort (CRIC) study of chronic kidney disease,[15] as well as in other cohorts and intervention studies. Newer versions of this device use a cuff and tonometer system to record simultaneous pressure waves.[16] Published reproducibility of the PWV with the SphygmoCor, as judged by Bland-Altman plot analysis, is good.[17]

Mechanotransducer-based techniques (eg, Complior, ALAM Medical, Vincennes, France) use similar principles but allow simultaneous measurement between sites with distention sensors. The Complior software provides an online pulse-wave recording and automatic calculation of the PWV.[18] This device has been used extensively in epidemiologic studies in Europe and has provided much of the early outcome data

relating PWV to CVD risk. The published reproducibility of the PWV with the Complior, as judged by Bland-Altman plot analysis, is good.[19]

Other tonometry-based devices (eg, PulsePen, DiaTecne, Milan, Italy) use an ECG signal and a handheld tonometer (similar to the SphygmoCor) to perform cfPWV measures. The PulsePen has been used in the Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population (PARTAGE) study conducted in elderly patients in France and Italy.[20] The reproducibility of the PulsePen, as judged by Bland-Altman plot analysis, is good.[21]

Still other tonometry-based devices (eg, those used by Cardiovascular Engineering, Inc, Norwood, MA) use a custom device to measure PWV with tonometric methods. The system uses the foot-to-foot measure of carotid and femoral pressure waveforms, with distance measures to the carotid artery site and femoral artery site calculated from the sternal notch. The ECG QRS complex is used as the timing onset point, and the elapsed time to the carotid pressure waveform foot and the femoral pressure waveform foot is calculated and divided into the distance measurement. This system has been used in the Framingham[22] and Reykjavik[23] studies, as well as other cohorts and intervention trials. Reproducibility of the PWV by this method is reportedly good (Gary F. Mitchell, MD, Cardiovascular Engineering, Inc, Norwood, MA; personal communication, June 1, 2015).

Devices Using Cuffs Placed Around the Limbs or the Neck That Record Pulse-Wave Arrival Oscillometrically

Oscillometry-based devices (eg, VP1000, Omron Healthcare, Kyoto, Japan) rely on 4 oscillometric cuffs placed on both arms (brachial) and ankles to calculate brachial-ankle PWV (baPWV; measured in meters per second). It also provides an ankle-brachial index (ratio of systolic pressure in the ankle to that of the brachial artery; a marker of peripheral arterial disease when this ratio is <0.9). Newer models (eg, VP2000) have additional probes that can be secured in place (with straps) that detect carotid and femoral pulses simultaneously (ie, both probes capture the same pulse wave) by tonometry. ECG leads are attached, as is a phonocardiographic microphone (whether the measurements are being done by oscillometry or tonometry). The subject's age, height, and sex are entered into the software, and the distance estimate is calculated with the use of statistical norms (based on Japanese individuals). The Omron device has been used in prospective observational studies, mainly in Asia, and for independently predicting loss of kidney function,[24] CVD,[25] and all-cause death.[26] Published reproducibility of the PWV with the VP1000, as judged by Bland-Altman plot analysis, is good.[27]

Cuff-based devices (eg, Mobil-O-Graph, IEM, Stolberg, Germany) capture brachial blood pressure (BP) and brachial waveforms (casual and at 24 hours) to estimate central aortic pressures and to estimate cfPWV.[28,29] The Mobil-O-Graph 24-hour pulse-wave analysis ambulatory BP measurement device uses a proprietary algorithm to obtain conventional brachial BP readings, after which the brachial cuff is inflated to the diastolic BP level and held constant for ≈10 seconds to record the pulse waves. Subsequently, central pressure curves are obtained with the use of a transfer function. To estimate aortic PWV, several parameters from pulse-wave analysis, along with wave separation analysis, are combined in a proprietary mathematical model incorporating age, systolic pressure, and aortic characteristic impedance.[30] The Mobil-O-Graph aortic PWV values have been validated by direct intra-arterial measurement in the catheterization laboratory.[31] Reproducibility of the Mobil-O-Graph, as judged by Bland-Altman plot analysis, is good.[32]

Some cuff-based devices (eg, Vasera, Fukuda Denshi, Tokyo, Japan) use cuffs on all 4 limbs and gate the timing for the pulse-wave arrival at the ankle relative to the heart using phonocardiography through a small microphone taped onto the chest.[33] In addition to the cardio-ankle vascular index, which is derived from the cardio-ankle PWV, it provides an ankle-brachial index. This device has been used mainly in Japan for longitudinal studies of dialysis patients[11] and in community studies of cognitive decline.[34] Reproducibility of the Vasera, as judged by Bland-Altman plot analysis, is good.[35]

Ultrasonographic Approaches

Ultrasonography can be used to assess vessel distention and derived stiffness indexes or flow waveforms to calculate PWV. Distention waveforms can be assessed with ultrasound transducers at a variety of locations, but often the carotid and femoral sites are used. Although some parts of the aorta itself are assessable, measurements in the thoracic aorta are technically challenging. An average change in cross-sectional area of a vessel can be derived from the distention waveform with dedicated software (eg, ARTLAB, ESAOTE, Genoa, Italy). Using a value for the pulse pressure (PP), the operator can determine distention and compliance. Brachial artery pressure often is used rather than local PP, which may introduce inaccuracies, as may any delay between distention and BP assessment. Pulse-wave speed (c) and other indexes of elasticity such as incremental elastic modulus can also be derived, as discussed earlier. It is worth noting that most ultrasonographic systems and software produce a time-averaged waveform, and mathematically, this will yield different values for stiffness indexes compared with calculating distention beat by beat and then averaging.

In addition, ultrasonography is used to assess local (cross-sectional) distensibility of vessels such as the carotid artery. B-mode ultrasonography, video analysis, and echo-tracking methodologies are commonly used approaches.[36,37] The online-only Data Supplement (Section 6) has more discussion of this aspect and device comparisons (Table 6.4 in the online-only Data Supplement).

Doppler ultrasonography may be used to record flow waveforms from accessible sites from which PWV can be estimated in a manner similar to PWV based on pressure waveforms. Waveforms may be recorded either sequentially with ECG gating or simultaneously.[38] Typically, 1 ultrasound transducer is clamped to the left side of the neck to insonate the site of the left subclavian artery or carotid artery, and the second transducer is secured on the abdomen, insonating the abdominal aorta above the bifurcation. Distance is measured from the suprasternal notch (SSN) to the location of the second transducer. This can be challenging because the angle of insonation makes it difficult to reliably determine where the

abdominal aorta is being interrogated in most (obese) people. The foot of the flow wave from each of the recording sites is used, and the time elapsed in milliseconds is calculated. There is no set duration of recording, but averaging several beats (commonly 5–10 beats) is beneficial to increase the accuracy of the measurement.[39] Identifying the foot of the flow wave can be more challenging than identifying the foot of a pressure wave. However, such techniques have shown independent predictive value for cardiovascular outcomes and death in longitudinal studies of diabetics,[39] the healthy elderly,[40] and a general population.[41] Published reproducibility of ultrasonography-based PWV, as judged by Bland-Altman plot analyses, is good.[42,43]

MRI-Based Approaches

MRI can be applied in much the same way as ultrasonography to determine distention-based indexes or PWV. It has the advantage of being able to assess almost any vessel and providing more accurate distance and area estimates (Vessels can always be "cut" in a perpendicular manner). However, these advantages are offset by poorer time and spatial resolution and cost.

Phase-contrast MRI (PC-MRI) can be used to acquire blood flow velocity maps along any given anatomic plane. When the gradient direction is applied exactly perpendicular to the cross-sectional vessel plane ("through-plane" velocity encoding), flow can be measured through the vessel cross section. Such an approach can be used to compute the time delay between the onset of flow in the ascending and descending thoracic aorta, which can be simultaneously interrogated in cross section in a properly prescribed anatomic plane. Alternatively, the gradient direction can be prescribed in plane with the vessel flow axis, allowing the acquisition of a velocity map along the length of the vessel. This approach allows the measurement of the spatiotemporal flow profile along the length of the vessel, thus allowing the computation of PWV. This approach can be easily applied to the thoracic aorta in the "candy-cane" plane.

PC-MRI sequences require a user-defined velocity-encoding sensitivity, which should be as low as possible to minimize noise during the acquisition yet higher than peak flow velocity in the region of interest to avoid aliasing. Although velocity-encoding sensitivity should be tailored to individual measurements, a velocity-encoding sensitivity of 130 to 150 cm/s allows adequate interrogation of thoracic aortic flow in most cases. PC-MRI data are acquired over several cardiac cycles, and consistent cardiac timing in each cycle is assumed. Adequate PC-MRI flow measurements require careful attention to technical details, including the recognition and minimization of sources of error such as phase-offset errors caused by inhomogeneities of the magnetic field environment (short-term eddy currents),[44,45] signal loss resulting from turbulent flow, partial volume averaging resulting from limited spatial resolution, and signal misregistration caused by in-plane movement of the aorta and pulsatile flow artifacts. The temporal resolution of PC-MRI flow measurements should be maximized, which requires data collection over multiple cardiac cycles. This is usually achieved by prolonged (several minutes) acquisitions during free breathing. Various alternative techniques have been proposed for fast, real-time assessments of PWV.[46–49] More research is needed into the optimal algorithm to measure the time delay between the foot of the flow waves with PC-MRI.

A second approach to measure arterial stiffness with MRI involves the assessment of arterial distention, which can be paired with pressure measurements to obtain local arterial compliance and distensibility. Steady-state free-precession techniques provide high contrast between the arterial lumen and arterial wall and allow automatic segmentation of aortic lumen throughout the cardiac cycle. Such approaches can be used to assess ascending aortic properties as long as simultaneous (or quasi-simultaneous) central pressure recordings are performed. Unfortunately, tonometric arterial pressure recordings are difficult within the MRI suite because available tonometry systems are not MRI compatible. Good reproducibility of PWV by PC-MRI has been reported, with intraclass correlation coefficients of ≈0.90.[50]

Many of the devices reviewed in this section can also be used to capture waveforms for central aortic pressure-wave analysis. Section 4 in this executive summary and Section 4 in the online-only Data Supplement provide greater detail.

Regardless of the approach used, it is critical to include an accurate measurement of BP at the time of stiffness measurement because mean arterial pressure (MAP) is an important determinant of stiffness (Section 7 and Recommendation 7.1). Reproducibility is generally good, and most devices and approaches have been in use for at least a decade. Other approaches to measuring arterial stiffness are covered in Section 2 in the online-only Data Supplement.

Section 3. Why Is Arterial Stiffness Important?

Recommendation

3.1. It is reasonable to measure arterial stiffness to provide incremental information beyond standard CVD risk factors in the prediction of future CVD events (*Class IIa; Level of Evidence A*).[10]

Arterial Stiffness as a Predictor of Future Cardiovascular Risk

Stiffening of the central arteries has a number of adverse hemodynamic consequences, including a widening of PP, a decrease in shear stress rate, and an increase in the transmission of pulsatile flow into the microcirculation. These effects have a number of detrimental consequences that may, in part, explain mechanistically why stiffness is a predictor of risk. Numerous studies involving various disease-specific and community-based cohorts have demonstrated that higher cfPWV is associated with increased risk for a first or recurrent major CVD event.[9,10] Consideration of cfPWV substantively reclassifies risk in individuals at intermediate risk for CVD, suggesting that consideration of cfPWV provides novel and clinically relevant information beyond that provided by standard risk factors.[10,22] In addition, small studies have demonstrated that persistent elevation of cfPWV during treatment for hypertension or CVD is associated with high risk for an adverse outcome in those with established disease.[51,52] The added benefit

of cfPWV in risk prediction models may be a manifestation of the relatively modest relation between cfPWV and standard risk factors other than age and BP.[53] In a recent individual-participant meta-analysis, higher cfPWV was shown to be associated with increased risk for coronary heart disease, stroke, and composite cardiovascular events. Importantly, relative risk was strongest in younger individuals, in whom an opportunity exists for early identification, lifestyle modification, and possible mitigation or prevention of further potentially irreversible deterioration of aortic structure and function.[10]

Hypertension

The association between arterial stiffness and hypertension is well established.[54–58] There is a widely held belief that increased aortic stiffness in hypertensive individuals is largely a manifestation of long-standing hypertension-related damage that stiffens the large arteries. A recent analysis from the Framingham Heart Study found that higher arterial stiffness, as assessed by cfPWV, was associated with BP progression and incident hypertension 7 years later.[54] However, higher BP at an initial examination was not associated with progressive aortic stiffening, suggesting that aortic stiffness is a cause rather than a consequence of hypertension in middle-aged and older individuals. These results and several additional studies provide strong evidence in support of the hypothesis that arterial stiffness represents a cause rather than a consequence of hypertension and underscore the importance of better defining the pathogenesis of aortic stiffening.[55–58]

High aortic stiffness is associated with increased BP lability.[59–61] A stiffened vasculature is less able to buffer short-term alterations in flow. Increased aortic stiffness is also associated with impaired baroreceptor sensitivity.[59,62–64] Together, these limitations may result in potentially marked alterations in BP as cardiac output changes during normal daily activities such as changes in posture and physical exertion.[65]

Cardiac Disease

Excessive arterial stiffness represents a compound insult on the heart. Aortic stiffening increases left ventricular (LV) systolic load, which contributes to ventricular remodeling and reduced mechanical efficiency. This leads to an increase in myocardial oxygen demand,[66] compounded by a reduction in diastolic coronary perfusion as PP widens and diastolic BP decreases with aortic stiffening.[67] Arterial stiffening may be associated with impaired measures of LV diastolic function,[68,69] which may increase cardiac filling pressure and further limits coronary perfusion. Finally, arterial stiffness is associated with atherosclerosis,[70–73] which may further impair ventricular perfusion, possibly leading to catastrophic reductions in ventricular function during ischemia.[67]

Arterial stiffness is associated with diastolic dysfunction and diastolic heart failure resulting from direct effects of abnormal load and loading sequence on myocyte contraction and relaxation and indirectly through ventricular hypertrophy.[69,74–78] Diastolic dysfunction increases filling pressures and thus may increase load on the atria, which will contribute to atrial hypertrophy and fibrosis and ultimately to atrial fibrillation.[79] Arterial stiffness is independently associated with an increased risk of heart failure[80] and is increased in patients with established heart failure regardless of whether LV function is preserved or impaired.[81–83]

Peripheral Vascular Function

Arterial stiffness (arteriosclerosis) is associated with atherosclerosis, although the association is not strong and the 2 processes should be viewed as distinct pathophysiological entities. Aortic stiffening may increase the risk for development of atherosclerosis as a result of atherogenic hemodynamic stresses associated with a stiffened aorta, including increased pressure pulsatility and abnormal flow patterns in large arteries, with high flow and shear stress during systole, and with stasis, or flow reversal, during diastole.[84] Arteriosclerosis also has important implications for the structure and function of the microcirculation.

Aortic stiffening leads to loss of normal impedance mismatch between the normally compliant aorta and stiff muscular arteries. Loss of impedance mismatch reduces the amount of wave reflection at the interface between aorta and proximal branch vessels and therefore increases transmission of excessive pulsatile energy into the periphery, where it may cause damage.[23,85,86] Increased aortic stiffness and excessive pressure pulsatility are associated with increased resting microvascular resistance and markedly impaired postischemic reactive hyperemia in the forearm.[87] Resistance vessel remodeling, as assessed by the media-to-lumen ratio, is more closely related to PP than mean pressure, suggesting that anatomic constraints may contribute to limited reactivity in remodeled vascular beds.[88–91] Indeed, a recent study demonstrated a significant relationship between aortic PWV and the media-to-lumen ratio of small resistance arteries in a cohort of hypertensive patients after adjustment for age and BP.[92] Dynamic tone in small arteries is also affected by pressure pulsatility.[93–96] As a result, vascular resistance in autoregulated organs such as the kidney and brain may depend on PP and MAP. If resistance vessel tone increases in response to PP at a constant level of mean pressure, flow will decrease as resistance increases. Hence, alterations in the relation between mean and PP could lead to dissociation between mean pressure and resistance and interfere with the autoregulation of flow. Beyond midlife, PP increases rapidly as mean pressure remains constant or decreases, potentially putting autoregulated organs at risk for relative ischemia.

Central Nervous System

High-flow organs such as the brain and eye are particularly sensitive to excessive pressure and flow pulsatility.[97] High local blood flow is associated with low microvascular impedance, which facilitates penetration of excessive pulsatile energy into the microvascular bed.[23] This may contribute to repeated episodes of microvascular ischemia and tissue damage and manifests as white matter hyperintensities, clinically unrecognized focal brain infarcts, and tissue atrophy, each of which contributes to cognitive impairment and frank dementia.

Aortic stiffening is also associated with increased risk for large-vessel stroke, either ischemic or hemorrhagic.[98,99] This may be mediated through atherosclerosis, with increased stiffness contributing to both atherogenesis and risk for plaque rupture[100]; through atrial enlargement and fibrosis, which

can trigger atrial fibrillation, providing a cardiac source for embolus[79]; or through diastolic flow reversal in the aorta, which could disrupt and redirect plaque from the distal arch into the carotid circulation.[101] Excessive pressure pulsatility can also predispose to large-artery dissection or rupture of intracranial aneurysms, leading to hemorrhagic stroke. In addition, increased aortic stiffness is associated with BP lability, which is a risk factor for incident stroke.[102]

Arterial stiffness is also associated with impaired cognitive function in selected[103–107] and community-based samples.[23,108–112] In light of the generalized insult on the brain vasculature that occurs, it is perhaps not surprising that aortic stiffness is associated with a broad spectrum of cognitive sequelae and has been established as a risk factor for both vascular and Alzheimer-type dementia.[113]

Kidney Disease

Like the brain, the kidneys are low-impedance organs that are exposed to obligate high flow throughout the day. In addition, the unique structure of the microvasculature in the kidney, with resistance vessels on either side of the glomerulus, markedly increases pressure in the glomerulus to nearly aortic levels. In the presence of increased aortic stiffness, the microvasculature of the kidney is exposed to excessive pressure and flow pulsatility, which can damage the glomerulus, leading to proteinuria and loss of function.[114,115] Recently, increased renal pulsatility has been correlated with cardiovascular and renal outcomes.[116] Numerous studies have demonstrated modest but robust associations between increased PP or PWV and reduced glomerular filtration rate (GFR) or proteinuria.[117–123] However, relations between estimated GFR and stiffness measures are less robust in some studies after adjustment for potential confounders. In a study that measured GFR directly, higher PP was associated with reduced measured GFR.[124] Importantly, PP was not related to GFR estimated from serum creatinine in that study, indicating that relations between PP and estimated GFR may be obscured in older individuals in whom loss of muscle mass may reduce the accuracy of creatinine-based GFR-estimating equations.[125–127] Given that the prevalence of abnormal aortic stiffness is heavily age dependent, the burden of stiffness-related kidney damage may be underestimated when estimated GFR is used as a surrogate for kidney function.

Thresholds and Normative Values for Risk Assessment

cfPWV was included in the 2007 European Society of Hypertension/European Society of Cardiology guidelines for the management of hypertension[128] in which a fixed cutoff of 12 m/s was proposed, indicating subclinical organ damage. This was modified by a recent expert consensus, which took into consideration a new distance calculation methodology and recommended a new 10-m/s threshold (derived by multiplying 12 m/s by 0.8 and then rounding up).[129] Although attractive because of the simplistic approach, risk estimation based on fixed thresholds has several limitations, not least of which are the relatively continuous relationship between risk and cfPWV and the failure to consider factors such as transient elevation of MAP, which may confound cfPWV values because of nonlinear stiffness of the aortic wall.

A single threshold also fails to take into consideration the dominant effect that age has on PWV. A cfPWV value of 12.1 m/s may convey different prognostic information in an 80-year-old person and in a 25-year-old person. Variability of cfPWV with age prompted an interest in attempting to establish reference values for various segments of the population.[129,130] The European Network for Non-invasive Investigation of Large Arteries assembled the Reference Values for Arterial Stiffness' Collaboration, which was tasked with generating reference and normative values for cfPWV. The cohort included 11 092 individuals who yielded reference values of cfPWV stratified by age groups (<30, 30–39, 40–49, 50–59, 60–69, and >70 years). In addition, from the subset of individuals who had optimal or normal BP and no additional cardiovascular risk factors, normative values for cfPWV were generated according to age groups.[131] However, it should be emphasized that these normative and reference values are applicable predominantly to measurements performed with the aforementioned methodologies.

Despite the attractiveness of age-relative normative thresholds, it is important to recognize that an age-related increase in cfPWV should not necessarily be viewed as inevitable or indeed a normal part of the aging process. Although cfPWV increases exponentially with aging in most populations, it appears to increase much less rapidly in truly rural or indigenous populations,[132,133] as Truswell et al[134] reported for BP in the 1970s. The observation that cfPWV increases more modestly with age in lower-risk individuals suggests that a major part of age-related stiffening is pathological and that therefore it may not be appropriate to use age-specific thresholds for risk estimation.

Section 4: Arterial Stiffness, Wave Reflections, and LV Afterload

Recommendations

4.1. Both time-resolved central pressure and central aortic flow should be quantified when assessing LV afterload as either an exposure for a cardiovascular outcome or a target for intervention (*Class I; Level of Evidence C*).

4.2. The use of pressure-flow analyses, which are considered the gold-standard assessment, is recommended to determine LV afterload (*Class I; Level of Evidence A*).[135,136]

4.3. Effective arterial elastance (Ea) should not be used as an index of pulsatile LV afterload or arterial stiffness because it represents a poor index of pulsatile load and is not significantly influenced by arterial stiffness (*Class III; Level of Evidence B*).[137,138]

4.4. The use of wave separation analysis, as opposed to aortic AIx, is recommended when investigations are focused specifically on the role of wave reflection as either an exposure for a cardiovascular outcome or a target for intervention (*Class I; Level of Evidence B*).[41,139,140]

The mechanical "afterload" imposed by the systemic circulation to the pumping LV is the aortic input impedance, is an important determinant of normal cardiovascular function, and is a key pathophysiological factor in various cardiac

and vascular disease states. In the presence of a normal aortic valve, LV afterload is determined largely by the elastic properties (arterial stiffness), arteriolar caliber, and wave reflection characteristics of the arterial tree (arterial load).[136] Arterial load is complex and time varying and cannot be characterized by a single number or index. LV afterload is composed of a steady component and a pulsatile component and can be described by the following indexes: systemic vascular resistance, aortic characteristic impedance, total arterial compliance, wave reflection amplitude, and reflected wave TT.

Systemic vascular resistance, the steady component of LV afterload, is determined largely by arteriolar caliber and number. Pulsatile load, in contrast, is determined by the hemodynamic function of conduit arteries, which in turn depends on their geometry and wall stiffness. Although brachial arterial pressure (systolic, diastolic, and pulse pressures) is often used as a surrogate of arterial function and LV afterload in clinical practice, LV afterload cannot be fully described in terms of peripheral pressure alone and needs to be assessed in the frequency domain from central aortic pulsatile pressure-flow relations[141,142] or estimated in the time domain from the aortic pulsatile pressure alone.[3]

Furthermore, it should be recognized that afterload affects, in a reciprocal fashion, the pressure and flow waves generated by the LV and that pressure and flow waves not only are dependent on load but also are strongly influenced by LV structure and function.

Flow can be measured invasively with a flow wire or noninvasively with MRI or with pulsed-wave Doppler echocardiography interrogating the LV outflow tract. Central aortic pressure can be measured invasively with a pressure-sensing catheter or wire or via radial arterial tonometry and a general transfer function, which synthesizes a central aortic pressure waveform,[3] or by carotid arterial tonometry. For noninvasive assessments, calibration of central pressure waveforms should be performed with the use of peripheral diastolic pressure and MAP, which (in contrast to systolic pressure) remain relatively constant throughout the arterial tree.[135] To obtain central aortic pressure waveforms, calibration of the radial artery waveform is performed with peripheral systolic and diastolic pressures.[1,3]

An increase in the pulsatile component of afterload causes an undesirable mismatch between the LV and the arterial system, increasing myocardial oxygen demand and decreasing cardiac efficiency.[66,143] These changes in ventricular/vascular coupling promote the development of LV hypertrophy and often lead to both systolic and diastolic myocardial dysfunction.[69,144–146] In health, there is an increase (or amplification) in the PP as the pulse wave travels from the proximal aorta to the periphery. Increasing aortic wave reflection amplitude increases aortic systolic pressure, decreases the gap between central and peripheral PPs, and dampens (or reduces) this amplification. Decreasing wave reflection amplitude with antihypertensive therapy or exercise conditioning increases the gap (and amplification) and reduces target-organ damage.[147] Conversely, a reduction in PP amplification is associated with overt target-organ damage and independently predicts future cardiovascular mortality.[148,149]

Thus, PP amplification has been proposed as a potential mechanical biomarker of cardiovascular risk and global arterial function. As a result of systemic changes in arterial stiffness and wave reflections coupled with changes in heart rate, brachial BP is not an accurate predictor of LV load and central hemodynamic burden. Moreover, the beneficial reduction in ascending aortic systolic pressure and PP with various therapeutic approaches is often underestimated by cuff measurements of brachial artery pressure.[3,150]

Once measures of central aortic pressure and flow are obtained, they can be modeled to assess steady and pulsatile LV afterload and the amplitude and timing of wave reflections. An important relationship in the aorta is the pressure adaptation to pulsatile flow. When there is no influence on this relationship from wave reflections, as occurs early in early systole, pressure and flow waveforms look very similar. The relationship of aortic pressure and flow in the absence of wave reflections is called the characteristic impedance and is typically depicted as Zc (or Zo). An illustration of this relationship is shown in Figure 4.3 in the online-only Data Supplement. After arrival of the reflected wave in the central aorta, the pressure and flow waveforms diverge because the reflected wave increases systolic pressure and reduces flow during deceleration. The degree of this divergence is associated with the local Zc and reflection site distance.[151–153] This principle is used in linear wave separation analysis, which decomposes pressure and flow waveforms into their forward (incident) and backward (reflected) components. Reflection magnitude is expressed as the ratio of the amplitudes of reflected/forward pressure waves,[153] whereas reflection index, or AIx, is the ratio of the amplitude of the reflected wave and central aortic PP. Reflected pressure waves arriving at the proximal aorta increase the late systolic load of the LV, thus altering the loading sequence. Increased wave reflection amplitude and an LV loading sequence characterized by late systolic load have been shown to cause myocardial hypertrophy,[144,154,155] myocardial fibrosis,[154] and systolic and diastolic myocardial dysfunction[74,76,156–162] and to strongly predict an increased risk of future heart failure.[139,161] Increased wave reflections have also been shown to predict all-cause 15-year mortality.[41]

Because invasive recordings of central aortic pressure and flow waves and pulse-wave analysis can be made in only a select number of patients in the catheterization laboratory, techniques have been developed recently that enable the noninvasive determination of the above variables[163,164] in large cohorts with similar results.[143,165–170] Some studies use the carotid artery wave as a surrogate for the central aortic pressure wave; others derive it from the radial artery wave using a general transfer function. Briefly, radial artery pressure waves are recorded at the wrist with the use of applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms are acquired and an ensemble is averaged, a validated general transfer function is used to synthesize the central aortic pressure wave noninvasively. To obtain the general transfer function, computer software performs a Fourier series representation of the radial artery waveform into harmonic components of amplitude and phase angle. These harmonics are then adjusted with the use of data obtained from

previous invasively measured aortic pressure waves to obtain the noninvasive synthesized central aortic pressure wave.[3] Two visible demarcations usually occur on the initial upstroke of the central aortic pressure wave in middle-aged and older individuals: the first shoulder and the inflection point. These demarcation points occur at an earlier age in patients with hypertension. The first (or early) shoulder is generated by LV ejection and occurs at peak blood flow velocity, whereas the inflection point occurs later and denotes the initial upstroke of the reflected pressure wave; this wave represents the second (or mid to late) systolic shoulder.[3,171–175] The first shoulder is an estimate of forward traveling-wave amplitude, and the second shoulder is an estimate of reflected-wave amplitude. The characteristics of the reflected wave depend on the physical properties (stiffness, taper, and branching) of the entire arterial tree (elastic plus muscular arteries and arterioles), PWV, the round-trip travel time of the wave from the heart to the periphery and back, and the distance to the major "effective" reflecting site in the lower body.[3,171–175]

Ea, computed as the ratio of end-systolic pressure to stroke volume, was proposed as a lumped parameter of resistive and pulsatile LV afterload[176] and is increasingly being used because of the simplicity of its computation. However, Ea is almost entirely determined by the product of heart rate (a cardiac property) and systemic vascular resistance[138,177] and, despite its name, does not reflect or characterize pulsatile LV afterload.[137,138] Ea does not represent a physical elastance (or compliance) and is not related to arterial stiffness. Therefore, it should not be interpreted or used to measure pulsatile afterload or arterial stiffness.

Interventions that reduce arterial stiffness and wave reflections, the primary cause of elevated systolic BP and LV hypertrophy, include drugs prescribed for the treatment of hypertension and heart failure. These drugs are usually categorized as vasodilators, aldosterone blockers, β-blockers, and diuretics. Different cardiovascular drugs have different effects on arterial properties (structure and function) and wave reflection characteristics.[165,178–180] In most countries, thiazide diuretics are the cheapest antihypertensive drugs available. They are the recommended first-line treatment for hypertension in the United States (Seventh Report of the Joint National Committee).[181] Diuretics and pure β-blockers decrease BP but have little if any direct (active) effect on arterial properties and wave reflection characteristics. Selective and nonselective aldosterone blockers attenuate cfPWV and AIx[182,183] in select patient groups by increasing nitric oxide bioactivity and improving endothelial vasodilator dysfunction.[184] Vasodilating drugs such as hydralazine and dipyridamole primarily increase arteriolar caliber and therefore decrease peripheral resistance and MAP via their action on arteriolar smooth muscle cells with little effect on aortic wave reflections.[185] Nitrates primarily relax smooth muscle cells in large conduit muscular arteries and therefore decrease arterial stiffness and aortic wave reflection amplitude and duration and reduce central systolic and PP, with little change in brachial cuff systolic pressure and PP.[186–188] Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are the most commonly used vasodilator drugs. These drugs appear to have little direct effect on stiffness of elastic arteries such as the aorta independently of BP reduction,[3,180] although some studies question this finding.[189–191] A recent meta-analysis observed that angiotensin-converting enzyme inhibitor therapy improved the stiffening of arteries, as reflected by PWV, and reduced arterial wave reflections, as assessed by AIx, compared with placebo.[192] β-Blockers appear to show less benefit on central aortic pressure compared with angiotensin-converting enzyme inhibition (eg, in the Conduit Artery Function Evaluation study[193]), but less is known about newer β-blockers that feature either concurrent α-blockade (carvedilol) or nitric oxide stimulation (nebivolol).

Several nonpharmacological interventions reduce arterial stiffness and wave reflections, including aerobic exercise training,[194,195] dietary changes (including weight loss and salt reduction),[196–199] passive vibration,[200] and enhanced external counterpulsation treatment.[201] For maximum cardiovascular benefits, these interventions must be initially introduced immediately and continued over an extended period of time. Although the effects of exercise on arterial stiffness and wave reflections have been studied for more than half a century,[202] many aspects remain unclear. It appears that the effects depend on the type (aerobic or resistance), intensity, and duration of exercise (short or long term [endurance, training, conditioning]). Multiple studies attest to the benefits of regular aerobic physical exercise in advanced age, hypertension, DM, coronary artery disease, and heart failure; to the improvement in oxygen extraction from blood; and to the improvement in cardiovascular function that occur with exercise training. Cross-sectional studies of aerobic exercise–trained individuals are conflicting and have reported both reduced pressure[195,203,204] and increased pressure[205,206] from wave reflections. These differences in wave reflection characteristics and central aortic pressure may be linked to lower heart rates in the endurance-trained subjects. The increase in pressure is probably because of an increase in the first systolic shoulder resulting from an increase in peak aortic blood flow. Longitudinal exercise training studies are similarly somewhat conflicting and have noted improvements in pressure from wave reflections[194,207] or no change.[208] Although endurance exercise training has been shown to reduce arterial stiffness and to improve peripheral vascular tone and endothelial function, exercise training–mediated reductions in heart rate[209] and improvements in LV contractility[210] likely represent equipoise in their potential to detect a reduction in pressure from wave reflections consistently across studies. There is no doubt that weight loss and regular exercise lower LV afterload (static and dynamic components) and heart rate, enhance quality of life, and reduce morbidity and mortality from cardiovascular events.[211] In a recent review of the effects of diet and exercise on arterial stiffness in patients with elevated cardiometabolic risk from hypertension, signs of atherosclerosis, or kidney disease, Sacre and colleagues[212] noted that these nondrug interventions can improve arterial stiffness by several mechanisms. Aerobic exercise may do so by improving vascular smooth muscle cell relaxation through increased nitric oxide bioavailability and reductions in oxidant stress and inflammation. Among dietary approaches, although it has been shown so far that reductions in sodium intake are associated with reductions

in PWV, these seem to be due largely to the changes in BP that occur (although others have found a reduction in PWV independently of BP changes[213]). Sacre et al[212] also noted that increased sodium intake and caffeine supplements tended to promote arterial stiffness. People who exercise regularly are more likely than those who do not to control their weight and to control other risk factors for coronary and other vascular diseases. In older individuals, 1 year of exercise training was found to significantly improve physical fitness and lifetime risk for CVD without affecting endothelial function or arterial stiffness.[214]

Short-term resistance exercise imposes a very different stress on the cardiovascular system than aerobic exercise. Although aerobic exercise induces a volume load on the heart and other organs, resistance exercise imposes a pressure load. A single bout of resistance exercise increases pressure from wave reflections, and unlike aerobic exercise, resistance exercise increases aortic stiffness and reduces PP amplification.[215] The effect of habitual resistance exercise training on central aortic stiffness and pressure from wave reflections remains controversial. A recent meta-analysis concluded that high-intensity resistance exercise training is associated with increases in central aortic stiffness in those with lower baseline stiffness values.[216] Resistance exercise training was initially shown to increase pressure from wave reflections,[217] with subsequent studies noting no effect.[209,218–222]

Other aspects of ventricular-vascular coupling, including myocardial wall stress, are covered in Section 4 in the online-only Data Supplement.

Section 5. Arterial Stiffness in Children

Recommendation

5.1. Devices measuring stiffness in children should be validated in children (*Class I; Level of Evidence C*).

The participants of the major longitudinal studies of cardiovascular risk factors in children are too young to provide data linking cardiovascular risk factor levels measured in childhood to hard cardiovascular events in adulthood.[223]

However, there are correlations between known adult cardiovascular risk factors, high-risk conditions such as chronic kidney disease and DM, and novel risk factors with intermediate noninvasive measures of vascular health, which are linked to hard events in adults. In this section, we discuss the current evidence, with reference to the previous American Heart Association article on noninvasive measures in children.[224]

Arterial Stiffness, Cardiovascular Risk Factors, and High-Risk Disease States in Pediatrics

There are now sufficient data from studies such as the Bogalusa Heart Study to link cardiovascular risk factors measured in youth such as BP directly to estimated PWV in adulthood.[225] The Cardiovascular Risk in Young Finns study has also demonstrated higher adult PWV with clustering of risk factors in youth such as in the metabolic syndrome.[226] Conversely, clustering of advantageous risk factors (fruit and vegetable consumption) is associated with a lower PWV as an adult.[227] Low birth weight was associated with higher PWV in adulthood in a study that examined baPWV,[228] but an association was not found in a study that examined cfPWV.[229] These differences highlight the importance of standardization of measurements and that indexes of stiffness are not always interchangeable because they may convey different predictive values.

These observations led to interest in delineating the determinants of PWV in healthy children and adolescents. Two studies evaluated sex differences in PWV. One study found higher cfPWV and femoral-dorsalis pedis PWV in female subjects before puberty, with the difference for cfPWV disappearing after maturation, whereas femoral-dorsalis pedis PWV was higher in male subjects after puberty.[230] Higher values of baPWV were found in male subjects regardless of maturation level.[231]

Traditional cardiovascular risk factors have been found to influence PWV in youth. Children with elevated low-density lipoprotein cholesterol had significantly higher PWV compared with control subjects (4.72±0.72 versus 3.66±0.55 m/s),[232] and PWV increases across tertiles of ratio of triglycerides to high-density lipoprotein, a lipid parameter that reflects burden of small dense low-density lipoprotein particles.[233] Higher PWV compared with control subjects was found in adolescents with a family history of hypertension,[234,235] prehypertension,[236–238] and sustained hypertension.[236,237] Other cardiovascular risk factors such as psychosocial stress,[239–241] smoking,[242] low physical fitness[243,244] or physical inactivity,[245,246] and low dairy intake[247] have also been related to higher PWV in pediatric patients. However, the studies vary considerably in adjustments for confounding factors such as MAP, heart rate, and age, making interpretation of potential causality difficult.

Many data are also available to examine the relationship between obesity and PWV in the young. Two large studies with >600 subjects each demonstrated higher PWV in obese adolescents compared with their lean counterparts,[248] and the effect of obesity was independent of other cardiovascular risk factors.[249] Obesity-related metabolic syndrome clustering was also shown to result in higher PWV.[250] However, insulin resistance appears to play an independent role only for baPWV,[251,252] not for cfPWV.[253]

Because cardiovascular risk factors influence PWV, it is not surprising that higher PWV is found in children and adolescents with high-risk conditions. Youths with type 2 DM have higher PWV than both their lean and obese counterparts.[249] Surprisingly, subjects with type 2 DM have higher PWV than those with type 1 DM despite a shorter duration of disease.[254] In a study of 535 subjects with type 1 DM and 60 with type 2 DM, the higher PWV in subjects with type 2 DM was explained largely by increased central adiposity and higher BP.[254]

Pediatric patients with renal disease also demonstrate increased arterial stiffness, a potential mechanism for the observed increased in cardiovascular events in adults with kidney disease.[255] Children on dialysis have higher PWV than less severely affected patients[256] and control subjects.[257] Unfortunately, these adverse vascular changes may not normalize after renal transplantation.[258–260] However, children with glomerulonephritis and increased PWV saw normalization with recovery.[261] For this reason, there is hope that

treatment of inflammatory vasculitis such as that seen in HIV infection,[262] polyarteritis nodosa,[263] and Kawasaki disease[264] may result in a reduction of PWV, although these types of long-term interventional studies have not been carried out to date.

A number of studies have evaluated PWV in children with congenital heart disease. Not surprisingly, PWV is higher in pediatric patients after cardiac transplantation.[265] Increased PWV has also been demonstrated after repair of tetralogy of Fallot, which is hypothesized to be a risk factor for progressive aortic root dilation in these patients,[266–268] and in youth after arterial switch operation for transposition of the great vessels.[269] The largest amount of work has been done in patients after repair of coarctation of the aorta as a result of heightened concern for the role of arterial stiffness, manifested as increased PWV, in late complications such as hypertension[270–273] and premature CVD.[274] Data on other inherited disorders associated with increased arterial stiffness are less clear. One study of patients with Marfan syndrome found higher PWVs compared with control subjects,[174] whereas another small study of patients with Marfan syndrome (n=10 cases and 10 controls)[275] and a study of youth with neurofibromatosis type 1[276] found no differences. Clearly, larger studies of PWV in pediatric patients with these high-risk conditions should be conducted.

The use of these noninvasive intermediate end points to better risk stratify youth is essential because data linking childhood measures of cardiovascular risk factors to hard cardiovascular events in adults are lacking. Further studies correlating risk factors to vascular damage or other target-organ damage such as LV hypertrophy will provide evidence to pediatric practitioners faced with the challenge of implementing aggressive drug therapy in high-risk children. Assessing PWV in healthy children may also provide an ideal platform to identify novel mechanisms driving stiffness because the influence of traditional cardiovascular risk factors and atherosclerosis per se will be minimized.

Developmental Changes in Arterial Function in Childhood

Many investigators have found an increase in arterial stiffness from childhood to adolescence,[133,231,277,278] including large- and small-artery compliance.[279] Using MRI, Voges et al[280] found a decrease in descending aorta distensibility and an increase in PWV starting at 2.3 years of age. It appears that these must relate to changes in the vessel wall because vascular compliance is determined by both vessel size and distensibility of the wall and because the MRI study demonstrated a steady increase in cross-sectional area of the descending aorta (with a slight plateauing after 15 years of age).[280] Similarly, Senzaki et al[281] found that although arterial compliance increased from birth to 20 years of age, once normalized for body surface area to control for differences in arterial size, there was an overall decline over this period of time, although the rate of change was not constant, with the most rapid decline in compliance during periods of most rapid growth from 3 to 7 years of age. Whether there are sex-related differences in developmental changes in arterial stiffness is less clear. Ahimastos et al[230] found lower systemic arterial compliance and PWV in prepubertal girls compared with boys with no difference seen after puberty; Fischer et al[278] found sex differences in PWV both before and after puberty; and Voges et al[280] found no difference. Clearly, more studies defining normal levels for arterial function parameters and better data outlining the determinants of increased stiffness across the pediatric age groups are needed. Other vascular measures such as arterial distensibility, aortic AIx, ambulatory arterial stiffness index, normal values in youth, and technical considerations for measurement in children are discussed in Section 5 in the online-only Data Supplement.

Table 2. Recommendations for Grading Comparisons of Devices/Procedures for Measuring PWV With a Gold-Standard Device According to ARTERY Society Guidelines[283]

Accuracy	PWV Measurement
Excellent	Mean difference ≤0.5 m/s and SD ≤0.8 m/s
Acceptable	Mean difference <1 m/s and SD ≤1.5 m/s
Poor	Mean difference ≥1 m/s or SD >1.5 m/s

PWV indicates pulse-wave velocity.

Section 6. Validation of Arterial Stiffness Devices

Recommendations

6.1. The distance for the cfPWV should be determined by subtracting the SSN to the carotid site distance from the SSN to the femoral site distance or by multiplying the total directly measured distance by 0.8 (*Class I; Level of Evidence B*).[282]

6.2. Validation studies should be performed against invasive measurements. When this is not possible, new devices should be validated against a noninvasive device that has been used in prospective trials showing an independent prognostic value of PWV (Table 2) (*Class I; Level of Evidence C*).

In this section, we review the standards by which measurement methods of PWV are validated, discussing several methodologies for noninvasive PWV estimation.

Invasive Aortic PWV

This measurement has the advantage of being a simple, straightforward, precise, reproducible technique (measuring TT simultaneously or ECG-triggered and travel distance [TD] between 2 measurement sites).[282] Of note, pressure waves measured at different points in the aorta travel in only 1 direction along the aorta, yielding a physiologically correct measurement. However, true invasive aortic PWV has been reported rarely and for obvious reasons only in patients scheduled for coronary angiography.[282, 284–289] To date, 1 study has investigated its relationship to clinical outcomes.[286]

MRI-Based Aortic PWV

With this technique, TD can be measured very accurately with precise 3-dimensional imaging approaches. TT can be

estimated from dedicated sequences to derive flow signals. Flow signals as measured travel along the aorta in only 1 direction along a single path, yielding a physiologically correct measurement. However, the temporal resolution for TT assessment is somewhat lower compared with the other techniques, although this has been improved recently.[290] The reproducibility and accuracy with respect to invasive measurements may also depend on the methods used to determine TT,[291] and to date, there is no consensus on the best method to be used. Finally, there are no published studies relating MRI-based aortic PWV to cardiovascular end points.

Simultaneous Noninvasive Acquisition of Pressure Waves at the Carotid and Femoral Arteries

There are no studies showing the superiority of simultaneous measurements as opposed to sequential (ECG-triggered) recordings. When the sequential recordings are made a short time apart, heart rate variability or the change in the isovolumic period probably has no or only minor effects on measured TTs.[36]

Can Dedicated Devices for the Measurement of cfPWV Be Recommended as a Noninvasive Gold Standard?

Validation studies using invasive aortic PWV as reference are limited to patients undergoing cardiac catheterization on clinical indications, thus limiting such studies to a relatively small group of patients. When MRI-based aortic PWV is considered as reference, the dedicated MRI environment often will preclude simultaneous measurements (the same is true for invasive aortic PWV). In addition, some questions with respect to temporal resolution remain to be solved. For these reasons, it seems reasonable to perform validation studies against dedicated devices that have been used widely in prospective trials showing an independent prognostic value of cfPWV (Complior device, ALAM Medical; SphygmoCor device, AtCor Medical).

Standardization of Methods for Comparison of Devices

Because of the expansion of the field for noninvasive assessment of vascular function, devices are being constructed with varying pulse-sensing techniques and signal-processing algorithms. For proper and useful comparison of devices, there is a need for standardization of procedures and protocols. Such activities generally come from learned societies in the form of guidelines. For comparison of PWV devices, the Society for Artery Research has published specific guidelines for device validation.[291] There are tables for sample size (90 subjects selected with a minimum of 83 for data analysis), age range (at least 25 in the age ranges of <30, 30–60, >60 years), and exclusion criteria (eg, body mass index >30 kg/m^2, absence of sinus rhythm, significant arterial stenosis). There is also a specific description of the order of measurements between the devices to avoid the possibility of systematic errors. The results of device/method validation studies should be presented using the method of Bland and Altman[292] in which the difference between the values obtained with the 2 devices is plotted against the mean value of both devices. The plot then shows the mean of, and the difference between, the 2 methods or devices and includes ±2 SD as boundaries. Excellent, acceptable, and poor accuracy may be defined as shown in Table 2.[291] Moreover, any systematic bias with respect to one method will be evident from the plot. Special consideration should be given to the issue of TD estimation because different estimations between the devices will result in systematic overestimation or underestimation of cfPWV.

This protocol was recently used for the first time to validate a cuff-based device (SphygmoCor XCEL) for the detection of carotid femoral pulse TT, with the aim of providing cfPWV values similar to those obtained with a femoral tonometer.[16] When the cuff measurement of pulse TT was corrected for the distance between the femoral site and the position of the cuff on the upper thigh, both devices gave similar cfPWV (R^2=0.9) with a mean difference of 0.02 m/s and an SD of 0.61 m/s.

The Problem of Noninvasive Estimation of TD for cfPWV Measurement

In the measurement of cfPWV, the major source of inaccuracy lies in the determination of the TD of the pressure or flow waves.[293] First, measurements on body surface may not reliably represent the true length of the aortic and arterial segments, especially with obesity and when the arteries become more tortuous with age.[294] Second, by definition, cfPWV encompasses not only the aorta but also segments of the carotid artery and of the iliac and femoral arteries, which differ with respect to their elastic properties (and their local PWVs) from the aorta, even more so during aging. Moreover, the proximal part of the aorta (the most elastic one), which undergoes marked changes with aging,[294] is not covered. Finally, by definition, cfPWV encompasses the travel of the pulse wave up to the carotid artery and down the thoracic aorta at the same time. Thus, this is not a simple unidirectional path length,[129] thereby rendering all determinations of the "real" traveled path length somewhat elusive. Even sophisticated MRI-based distance measurements are valid only on the assumption that the velocities in the carotid artery and in the thoracic aorta are the same, which actually may not be the case. In animals, PWV in the carotid artery can be 2 to 3 m/s higher than in the aortic arch,[295] and in humans, the differences between aortic and carotid stiffness are higher in patients with hypertension and DM.[296] Whether these differences can affect the actual cfPWV by 2% or up to 10% has been discussed recently.[297] However, some standardization is obviously necessary, and comparisons of cfPWV with invasive PWV and MRI-determined PWV have been made. In 135 patients undergoing invasive coronary angiography, the subtraction method (SSN–femoral artery minus SSN–carotid artery) resulted in the smallest differences (0.2 m/s) between invasive aortic PWV and noninvasive cfPWW,[282] whereas the direct-distance method overestimated aortic PWV by 2.9 m/s. When the same TT (carotid-femoral TT derived from tonometry) was used and TD was measured with MRI (aortic arch to the femoral recording site minus carotid length from the origin to the recording site; again assuming equal velocities in carotid artery and aortic arch), the surface measurement closest to the MRI TD estimate was carotid-femoral minus SSN-carotid.[294] In another study,

with MRI used as reference for TD measurement (ascending aorta–femoral artery minus ascending aorta–carotid artery), the best estimate, as measured on body surface, was carotid-femoral distance multiplied by 0.8.[298] In all 3 studies, the direct carotid-femoral measurement led to a substantial overestimation of aortic PWV. Although conversion factors between the different cfPWV values obtained with different methods to assess TD are available from collaborative projects,[131] this panel recommends the use of either the subtraction method (SSN–femoral recording site minus SSN–carotid recording site) or the 80% method (80% of the measured direct distance between the carotid and femoral recording sites) to estimate TD for cfPWV. Additionally, the use of calipers may improve distance measurements, particularly in overweight or obese subjects.[299,300]

A comparison of the different methods and devices, accuracy, repeatability, and reproducibility is summarized in Section 6 in the online-only Data Supplement. In addition, a summary of the clinical validation, that is, which devices and techniques have been used in longitudinal clinical studies, again with a table, is provided in Section 6 in the online-only Data Supplement. Finally, a more detailed discussion of devices that provide an estimate of PWV from waveform analysis or local arterial stiffness is also provided in Section 6 in the online-only Data Supplement.

Validation of Devices to Measure baPWV

Repeatability and reproducibility can be investigated as usual, and such studies have been performed successfully.[27,35] TD for baPWV obviously can only be estimated because there is of course no direct unidirectional propagation of pressure or flow from brachial artery to ankle. The formula used in the systems is based on anthropometric data from Asians, which may differ from data in Western populations. Although the traveled path with baPWV clearly differs from pure aortic (invasive) PWV and from cfPWV through the inclusion of longer segments of muscular arteries, comparisons with invasive PWV[27] and cfPWV[301] have been made, showing a high degree of correlation. For noninvasive validation studies, systems that have been shown to predict cardiovascular outcomes should be used such as the VP1000 (Omron Healthcare) and the Vasera (Fukuda Denshi; Section 2).

Validation of Devices Providing Estimates of PWV From Single-Point Measurements

There is some interest in techniques estimating aortic PWV from brachial cuff-based waveform analysis (and clinical characteristics), which would simplify the procedure. In addition to reproducibility, such devices should undergo invasive validation when claiming to estimate aortic PWV and noninvasive validation against gold-standard devices measuring cfPWV. To date, invasive validation has been performed successfully for the Arteriograph (Arteriomed, Budapest, Hungary)[302] and the Mobil-O-Graph (IEM).[31] Clinical validation, that is, the prediction of cardiovascular events, is pending for the Arteriograph. One small study in patients with chronic kidney disease, National Kidney Foundation stages 2 to 4, has already shown the independent prognostic value of an estimated aortic PWV (measured with the Mobil-O-Graph device) with respect to mortality.[303]

Section 7. Factors Confounding Arterial Stiffness Measures and Practical Interpretation of Values

Recommendations

7.1. MAP and heart rate should be recorded at the time of an arterial stiffness measurement and taken into consideration when PWV data are analyzed as potential confounders (*Class I; Level of Evidence B*).[6,304]

7.2. The following are recommendations to enhance uniformity in arterial stiffness investigations:

- **a. The sites of measurement, for example, carotid-femoral, should be clearly stated in the Methods section (*Class I; Level of Evidence C*).**
- **b. It is reasonable to report how the distance measurement was performed in the Methods section (*Class IIa; Level of Evidence C*).**
- **c. It is reasonable to use calipers to obtain surface measurements to calculate distance for PWV (*Class IIa; Level of Evidence C*).**
- **d. Arterial stiffness measurements should be performed in duplicate in subjects in the supine position after a minimum of 10 minutes of rest, controlling the environmental noise and temperature as much as possible; the arterial stiffness measurement should be repeated a third time if the difference in the 2 measurements is >0.5 m/s using the median value (*Class I; Level of Evidence C*).**
- **e. Operators performing arterial stiffness measurements should be familiar with the equipment, should have been trained in the techniques, and should have demonstrated consistently reproducible results (*Class I; Level of Evidence C*).**

A number of physiological and methodological factors can influence and confound arterial stiffness indexes. These factors require due consideration to minimize their impact, to allow high-quality data to be obtained, and to allow correct interpretation of the data.

Physiological Confounders

The most significant physiological variable affecting arterial stiffness is the vessel distending pressure (MAP).[3,304–306] In contrast, PP provides an indirect index of large-artery stiffness because it depends on large-artery compliance, together with stroke volume and the influence of reflected pressure waves. As MAP increases, vessels stiffen, but in a nonlinear manner. Therefore, the measured value of stiffness will depend on, or be confounded by, the MAP, which should be taken into consideration. This is particularly relevant when populations with different BPs are compared or when the effects of antihypertensive agents are investigated.

The relationship between heart rate and arterial stiffness is less well defined, with short-term studies showing positive associations,[6,307,308] no association,[309,310] or even inverse associations[311] between increased heart rate and various measures of arterial stiffness, including PWV. These disparate results

reflect the fact that at least some of the studies may have been confounded by concomitant changes in MAP. Nevertheless, a recent study[312] demonstrated that, although heart rate exerts a minimal influence on PWV in the lower range of mean pressure values, an increase in heart rate results in a modest but significant increase in PWV at higher MAP values. Because BP and heart rate vary considerably both within and between individuals, both should be taken into consideration when measurements of arterial stiffness are undertaken.

To minimize such confounding effects, arterial stiffness should be assessed in a quiet, temperature-controlled environment. Participants should also refrain from alcohol, vasoactive medications, and vigorous physical activity ideally for 12 hours and large meals, caffeine-containing food and drinks, and smoking for at least 2 to 4 hours before the measurements. It is important that participants are allowed to rest in the supine position for at least 10 minutes to ensure hemodynamic stability. For menstruating women, attention should be paid to studying these subjects at a similar menstrual cycle phase.

Methodological Confounders

Although cfPWV is recognized as the gold standard for the noninvasive assessment of arterial stiffness,[36] arterial stiffness often is measured in alternative (or additional) vascular beds. For example, several noninvasive commercial devices assess baPWV. Compared with the carotid-femoral vascular bed, the brachial-ankle vascular bed encompasses additional arterial territories with different characteristics, different determinants of stiffness, and different influences of atherosclerosis. Conversely, invasive assessments of arterial stiffness and MRI-guided assessments of arterial stiffness often measure PWV across much shorter distances within the aorta. Indexes are not necessarily interchangeable, either physiologically or prognostically, and the methodology used should be clearly stated to assess PWV.

Even within a vascular bed, PWV may vary, depending on the specific device used to measure PWV. For example, Millasseau et al[313] assessed cfPWV with 2 commercially available devices in the same individuals. They found that the 2 devices yielded different values of PWV within the same individual. Importantly, the difference was attributable to the algorithm used by each device to derive the time of travel (foot-to-foot method with the SphygmoCor system versus maximum-slope method with the Complior system); thus, the same waveforms analyzed by the 2 devices could result in differences in PWV values of 5% to 15%.

Perhaps the most important methodological confounder of PWV measurements is calculation of the wave TD (Section 6). cfPWV is calculated as the distance traveled by the pressure wave divided by the time delay between the arrival of the pulse wave at the carotid and femoral sites (wave TT). For measurement techniques other than MRI, the TD is typically estimated from surface measurements between the recording sites. These measurements should be as accurate as possible because small errors in distance measurement may translate into much larger errors in the calculated PWV, up to 30% in 1 study,[314] and the measurement method and vascular territory should be clearly stated.

A tape measure is generally used, although calipers better minimize the impact of body contours and therefore are recommended. Different approaches are used to calculate wave TD, although the most common methods are the direct distance between the carotid and femoral sites (direct method) and the distance between the SSN and carotid site subtracted from the distance between the SSN and the femoral site (subtracted method), which better corresponds to the true anatomic distance assessed by MRI.[298] Weber et al[282] also found that the subtraction method was more closely related to true distance and that cfPWV determined with the device and the subtracted distance corresponded best to invasive assessment of PWV. Although a recent expert consensus document advised that distance should be calculated by multiplying the direct distance by 0.8 and conversion algorithms between the 2 methods have been developed,[315] they are likely to introduce further error. Therefore, the method of distance calculation should be clearly stated, and the subtracted distance is more anatomically true (Section 6 recommendation). How the application of different methodologies will relate to differences in risk prediction remains unclear.

Practical Consideration in Making Arterial Stiffness Measurements

Whenever tonometry or ultrasonography systems are used for sequential recording of pressure or flow waves with ECG gating, care has to be taken that cardiac rhythm is stable. In the presence of arrhythmias, measurements may be unreliable because of different intervals from the R wave of the ECG to the foot of the traveling wave.

In addition to physiological and other confounders of arterial stiffness measurements, there are a number of limitations associated with assessing arterial stiffness. Some of the techniques are highly operator dependent; thus, adequate training for the individuals making the recordings must be provided to ensure that high-quality data are obtained. Therefore, a period of familiarization with the measurement techniques is suggested, after which the trainee should obtain high-quality recordings in a minimum of 20 individuals to determine competency. In addition, the equipment required for these measurements is often expensive and not portable, limiting the use of some techniques for measuring arterial stiffness to specialist research settings. This is especially the case for MRI- and ultrasonography-based approaches, although a number of portable ultrasonographic systems are now available.

Section 8: Future Needs in Arterial Stiffness Study

Understanding how aging, stiffness, and BP interact over time is a complex conundrum. Aging-associated arterial changes and changes associated with hypertension (and early atherosclerosis and DM) are fundamentally intertwined at the cellular and molecular levels. In humans, other well-known risk factors (eg, excess food intake, altered dietary lipids and metabolism, smoking, and lack of exercise) likely interact with this arterial substrate that has been altered during aging, rendering the aging artery a “fertile soil” that facilitates the initiation and progression of these arterial diseases. Some lifestyle and pharmacological interventions have already

proved to be effective in preventing or ameliorating hypertension associated with aging. Although a number of small studies have suggested that various lifestyle interventions may produce BP-independent decreases in cfPWV, to date, the best evidence available in terms of therapeutic intervention suggests that angiotensin-converting enzyme inhibition may produce decreases in arterial stiffness beyond a BP-lowering effect.[316,317] Much larger meta-analyses of individual patient data will be required in the future to ensure that decreases in aortic PWV after therapy are truly BP independent. The cellular/molecular proinflammatory mechanisms driven by angiotensin II and other growth factors that underlie arterial aging are novel putative candidates to be targeted by interventions aimed at attenuating arterial aging and thus possibly attenuating the major risk factor for hypertension and atherosclerosis.[318]

Future investigations of the importance of arterial stiffness should address questions such as these:

- Do age changes within the arterial wall drive the age-associated increase in arterial stiffness, or does the increase in arterial stiffness with advancing age result from the age-associated increase in systolic BP?
- What is the natural history of PWV and BP vis-à-vis the rate at which PWV and BP increase with age?
- Will prevention or reduction of aortic stiffening provide substantial health benefits?
- What are the targets for intervention in a focused attempt to alter the nature of the arterial wall?
- Is it possible and safe to unstiffen the aorta independently of a BP reduction?
- Can the similarities in aging and stiffening of the arterial wall in animal models be used to guide human intervention trials, and will industry or peer review organizations consider these processes as potentially tractable and fund investigations into intervention trials? How would such trials differentiate the impact of a destiffening approach from a reduction in BP?
- Are there nondrug interventions that are likely to benefit arterial stiffening processes? At what age should such interventions be introduced?

Many of the above investigations will be facilitated by the development of cuff-based systems that will allow the measurement of hemodynamic parameters such as cfPWV, central BP, and AIx with as much ease and operator independence as oscillometric sphygmomanometry. Such systems have already been validated and have the facility for 24-hour ambulatory assessment of central BP (eg, the Mobil-O-Graph covered in Section 2). A logical progression would be to measure cfPWV with non–cuff-based systems. Such systems are already in development.[319]

The establishment of international reference norms for PWV across age and BP strata,[131] increasing recognition of the importance of central arterial stiffness as a consequence of aging and comorbidities,[8,97] potential improvements in understanding study outcome mechanisms when these measurements are incorporated,[51,193] recognition of the limitations of these measurements, and a spirit of cooperation between device manufacturers, the pharmaceutical industry, regulatory sponsors, payers, investigators, practitioners, and patients are necessary foundational elements in moving this process forward.

In addition, there are several gaps in the understanding of arterial stiffness in children:

- Lack of validation of measurement devices in children
- Lack of sufficient normative data by age/body size/pubertal status, sex, and race
- Lack of longitudinal data in healthy children and children with risk factors (DM, hypertension)
- Linking of arterial stiffness measurements to established pediatric intermediate target-organ end points

As this summary statement was nearing the final draft stage, a large patient-level (n=17 635) meta-analysis of arterial stiffness was published.[10] This study lends more support to the growing interest in arterial stiffness.

Overall Summary

Measuring arterial stiffness has been established clinically through longitudinal studies in which it has independently predicted death and standard cardiovascular end points. A number of devices and approaches have been developed to assess this parameter, providing both challenges and opportunities for the advancement of this aspect of the science of hemodynamics. Wider appreciation of the role of arterial stiffness beyond BP levels in clinical medicine and clinical research is an ongoing journey, and its indication for use in the clinic requires further study. We hope this summary statement represents a step forward in this journey.

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*Modest.

†Significant.

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*Modest.

†Significant.

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