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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KEY WORDS: AHA Scientific Statements ■ arterial stiffness ■ cardiovascular risk ■ guideline ■ large arteries ■ methodology ■ pulse-wave velocity

Online Supplement

Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness

A Scientific Statement From the American Heart Association

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SECTION 1: Arterial stiffness and underlying mechanisms

Authors: Alberto Avolio, Julio Chirinos, Edward Lakatta

1.0 What is arterial stiffness?

1.0.A General definition of material stiffness; stress-strain relationships-linear, nonlinear; clarify what arterial stiffness is not.

The definition of arterial stiffness involves the fundamental mechanical behavior of the material properties of the artery wall as well as the effect of wall properties on arterial function (1). The material properties are defined in terms of the fractional deformation (strain) due to an applied force per unit area (stress). The ratio of uniaxial stress to uniaxial strain is defined as the elastic (Young's) modulus (E), describing the stiffness of the material (2). For an isotropic material, E is constant in all directions. However, since arteries are essentially non-isotropic, E is not the same for circumferential or axial deformation (3). Conventionally, due to tethering, the deformation produced by the intra-arterial pressure (P) is considered to be mainly in the circumferential direction with change in diameter (D). Due to the cylindrical structure, the stress and strain can be represented by P and the fractional change in diameter ($\Delta D/D$) respectively. Hence, for constant length, the volume elastic modulus (or Peterson's elastic modulus, Ep) is defined as $Ep = P/(\Delta D/D$ (4)*)*. The important aspect of Ep as a stiffness parameter is that pressure and diameter are measurable quantities, which can be assessed non-invasively. For a linear elastic (Hookean) material the relation of stress and strain is constant, and the material has a single value of elastic modulus. However, the material properties of the artery wall change with applied force, hence the value of elastic modulus depends on pressure and consequently the state of distension (non Hookean material) (5). This is described as the incremental elastic modulus (E_{inc}), which is the tangent of the stress-strain curve at any specific point: $E_{inc} = \Delta P/(\Delta D/D)$ (Figure 1.1).

For any circular elastic structure, the circumferential wall tension (T) is related to the internal pressure by the Law of Laplace ($T = P.D/2$), assuming the wall thickness (h) is much smaller than D. Since the circumferential stress (S) is T/h, hence $\Delta S = \Delta P.D/2h$. The incremental stress, ΔS will cause an incremental circumferential strain equivalent to $\Delta D/D$. Thus $E_{inc} = \Delta P.D^2/(2h\Delta D)$.The quantity $\Delta P/(\Delta D/D)$ describes the bulk elastic modulus (K) for a given length

of vessel. Since, from basic principles of wave propagation in elastic media, pulse wave velocity (*PWV*) is related to bulk elastic modulus and blood density (ρ) [$PWV = (K/\rho)^{1/2}$] (1), the Moens-Korteweg relation is obtained which relates *PWV* to wall stiffness and geometry of the arterial cylindrical structure: $PWV = (E_{inc}.h/D\rho)^{1/2}$. This suggests that for a uniform arterial segment, PWV can be used as a surrogate of arterial stiffness, with the assumption that the relative wall thickness (*h/D*) remains constant.

The basic concepts outlined above have been developed and treated in early fundamental studies of arterial mechanics using isolated arterial segments assessing static and dynamic properties (2), pressure dependency of elastic properties (5;6), effect of smooth muscle activation (7). Recent studies and reviews have addressed the various indices of arterial stiffness that can be derived from measured quantities, essentially pressure and diameter (4;8;9). These studies provide extensive tabulated formulas and definitions.

1.0.A.i. Surrogate measures of arterial stiffness – and what arterial stiffness is not

Whereas arterial stiffness is explicitly defined in terms of arterial properties, surrogate measures related to pulse wave propagation are extensively used. The use of *PWV* is justified from basic relationships between physical quantities as expressed in the Moens-Korteweg relation (above). However, the use of systolic pressure augmentation (described as augmentation index *(AIx)*) as a surrogate of arterial stiffness requires particular clarification. *AIx* is computed from the pressure waveform using the pressure value at the first systolic shoulder (*P1)* above diastolic pressure *(Pd)* and relating the difference between systolic pressure *(Ps)* and *P1: AI = (Ps-P1)/(Ps-Pd).* The conceptual association between *AIx* and arterial stiffness is related to a stiffer vasculature having a higher *PWV* resulting in reflected waves arriving earlier in systole producing a higher relative a pressure augmentation. This mechanism does indeed play a role, but the degree of augmentation is also related to the intensity of peripheral wave reflection. Hence *AIx* cannot be used as a surrogate solely of arterial stiffness given the associated hemodynamic confounders. Furthermore, it is highly sensitive to heart rate (10).

1.0.B Application to material of artery wall; load bearing components; problems with heterogeneous properties of the arterial wall

The main load bearing components in large conduit arteries are elastin and collagen, with a much lower contribution by smooth muscle in the muscular arteries. Due to the anatomical arrangement of the elastin and collagen fibbers, elastin engages at low distension (hence at low pressure) and collagen and higher distension (and pressure) (11). However, although the lamella unit is proposed as being the fundamental structural element of elastin in the media of the artery wall (12), there is significant variation in human arteries compared to other species (13). In addition, there is substantial variation in the isotropic properties (6) and the contribution to wall stiffness of elastin and collagen along the aortic trunk (14). The adaptation seen with change in function is evident as the design of load-bearing components is optimized to minimize the amount of collagen recruitment and so stiffness, as is a necessary function in diving mammals (15).

1.0.C Non-linear stress-strain makes stiffness dependent on distension (i.e. arterial pressure).

An inherent feature of the mechanical properties of arteries is that the wall becomes stiffer with distending pressure (5). This is due to the increased amount of recruitment of stiffer collagen fibers with increasing distension. That is, the relationship of stress (pressure) and strain (diameter) is non-linear, with concavity toward the distension axis, such that there is diminishing distension with increasing force. Under stable conditions, the wall tension *(T)* is balanced by the transmural pressure *(P)* and diameter *(D)* ($T = P.D/2r$; as determined by Laplace's Law). The non-linear pressure-diameter relationship ensures that the linear tension-diameter relationship intersects at a single point on the pressure-diameter curve for a given pressure. This property is essential for the efficient mechanical operation of arteries as conduits for blood such that, with the maintaining of residual stress, the vessels do not collapse, and so always ensure patency for blood flow. Indeed, the non-linear elastic behavior of arteries has been described as a fundamental evolutionary property of arterial design for all vertebrates and invertebrates with closed circulatory systems (16).

1.0.D Hemodynamic effects of arterial stiffness

Arterial stiffness is a major determinant of vascular impedance, hence affecting the relationship between arterial pressure and flow (1). Since flow is determined by the local spatial *(x)* pressure *(p)* gradient *(dp/dx),* and the relationship between time *(t)* derivative of pressure, (*dp/dt*) and *dp/dx* is *dx/dt* (that is, wave velocity) the effect is that local wave velocity becomes a determinant of the instantaneous relationship between pressure and flow. For elastic conduits, the wave velocity is related to the stiffness of the wall through the Moen-Korteweg relationship (see Section 1.0.A.i). Thus, a stiffer wall will result in decreased vessel compliance, since a given increase in volume will generate a larger pulse pressure. That is, changes in wall stiffness will modulate the time-dependent relationship between pressure and flow rate. This is then expressed as changes in the frequency spectrum of arterial impedance (1).

1.0.D.i Effects on blood storage (compliance); determinant of pulse pressure

In a closed circulatory system, blood is stored in distensible compartments, with the venous system being responsible for buffering slow and relatively large changes in volume. However, the arteries, with the residual wall stress and elastic walls, are also able to buffer rapid changes in blood volume, such as occur during a single cardiac cycle. Hence, the value of elastic modulus of the artery wall is such that there is sufficient recoil so that the volume taken up during systole is returned during diastole, hence buffering the pressure due to pulsatile ejection. Thus increases in arterial stiffness will generate higher pulse pressure (*PP*) for similar stroke volumes (*SV*). Since the *SV* is the volume taken up by arterial distension and that flowing through the peripheral resistance (*R*), the ratio *SV/PP* is related to the total arterial compliance (*C*). In terms of arterial design, arterial stiffness is matched to obtain a value of *C* so as to optimize blood volume in the arterial compartment. For example, for maximal damping of *PP*, a large value of *C* would be required for a given *SV*, that is, a highly distensible system. However, this would store large volumes with slow time constant (the product *RC*) for recoil, and so would result in an inefficient circulation because of high inertia due to large blood mass to be displaced. These concepts are quantified in terms of the lumped parameter Windkessel model of the arterial system, consisting of a resistance (R) and a capacitor (C), and extended to a three element model by the addition of the characteristic impedance (*Zc*) (17). The model has been recently used to compute the intrinsic reservoir pressure due to the increase in aortic volume associated with cardiac ejection (18).

1.0.D.ii Effects of wave propagation – Pulse Wave Velocity- surrogate measure of arterial stiffness

Although the Windkessel model is adequate for lumped parameter estimation, it does not account for the finite time travel of the arterial pulse (17). This requires a spatially distributed system which is described in terms of wave propagation characteristics. Arterial stiffness affects PWV through the constitutive relation of wall stiffness, vessel geometry and blood density (Moens-Korteweg equation). In the large conduit arteries the small ratio of wall thickness in relation to diameter (*h/D*) makes changes in the material stiffness of the artery highly correlated with measured PWV. This is manifest by the similar nonlinear dependency of PWV on distending pressure. Hence the measurement of pulse propagation time over a known distance to compute PWV has been found to be a robust surrogate of arterial stiffness, in the absence of any confounding arterial malformation such as significant stenosis (9).

1.1 Mechanisms of arterial stiffness

Stiffening of arteries is generally associated with changes in the mechanical properties of the arterial wall. That is, alterations of stress/strain characteristics due to modification of properties of load-bearing structural components. The underlying mechanisms responsible for such modifications involve a complex interaction between the material properties of connective tissue and cell signaling pathways that alter the intrinsic and combined function of elastin, collagen, proteoglycans and glycoproteins of the extracellular matrix of the artery wall. A number of reviews address these issues (19-21), with the suggestion that the specific mechanisms can interact by way of positive or negative feedback pathways, depending on the extend of the stimulus (22).

Essentially, the underlying mechanisms can be considered as those related to elementary material properties, that is, “passive” mechanisms, and those that are regulated by cellular and molecular signaling where pathways can be interrogated, that is, “active” mechanisms.

1.1.A “Passive” mechanisms

1.1.A.i. Mechanical properties related to intra-arterial distending

The interaction of the loading function of the various wall components that bear the wall tension due to the distending pressure produces non-linear wall mechanical properties such that the wall becomes stiffer with increased distension. That is, the stiffness becomes pressure dependent (5). This is an important and intrinsic property of arterial design (16;23). Since an increase in distending pressure leads to an increase in stiffness, which then can potentiate a further increase in pulse pressure, this property constitutes a potential positive feedback mechanism (22) in relation to the relevance of arterial stiffness to cardiovascular risk, given the importance of systolic pressure, especially in age-related isolated systolic hypertension.

1.1.A.ii Effects of mechanical fatigue and fracture of elastin structures

All structural proteins in biology have elastic characteristics, with some rubber-like proteins (e.g. elastin, resilin) functioning with high resilience, large deformability (strains) and low stiffness, resulting in the ability to store elastic-strain energy (24). In arteries, this is a characteristic of both elastin and collagen, although elastin is much more extensible at lower strains than collagen. However, just as the efficiency of resilin determines the performance of insect wings during their lifetime (25), the efficiency of elastin is also a significant determinant of the overall stiffness of the arterial wall throughout life. From evolutionary considerations, it is reasonable to assume that the range of properties of elastic proteins will predispose elastic structures that are subjected to repetitive strains to a high resistance to fracture.

Due to the pulsatile nature of circulatory design, arteries are subjected to continuous and repetitive strain throughout life. In human tissue, radiocarbon prevalence data shows a range of half-life of 40-174 years (mean of 74 years) (26), making elastin the protein in the human body with the longest longevity. Having such a stable form with minimal turnover, the question is whether it can be subjected to the mechanical degradation effects of fatigue due to repetitive and unceasing strain throughout life. Such concepts are advanced as a mechanism of arterial stiffness due to elastin degradation, given the 30 million cycles per year to which the arteries are exposed (21) and so passive elastin degradation occurs with age, as distinct from active enzymatic processes (due to matrix metalloproteinase activity) (27). Evidence of increased degree of

disorganization and fracture of aortic elastin associated with the total number of cardiac cycles throughout life was found in a cross-sectional study of a range of species with a wide range of body size, heart rate and life span (28). This is complemented by structural alterations due to embryonic abnormalities affecting the structure of elastin throughout life, with increased predisposition to elevated arterial stiffness and associated cardiovascular risk (29). This has been recently confirmed in the aorta of mice with elastin haploinsufficiency where increased aortic stiffness precedes elevation of blood pressure during postnatal development (30). Other evidence of possible effects of fatigue on aortic elastin is obtained from the association of fragmentation and reduction of interlamellar fibers and the formation of aortic dissecting aneurysms (31). Recent investigations in the role of elastin in arterial stiffness of large arteries have suggested means of reversing alterations to elastic fibers as a therapeutic treatment for hypertension (32).

1.1.A.iii Effects of heart rate

The cardiovascular risk associated with elevated heart rate has been shown to be comparable to that associated with increased arterial pressure, where a 20% increase in cardiac death is associated both with a rise in heart rate of 10 beats/min, or an increase in systolic pressure of 10 mmHg (33). Although the underlying causes are mainly related to increased sympathetic activity, there is also evidence that elevated heart rate is independently associated with increased progression of arterial stiffness as measured by aortic pulse wave velocity (34). Underlying mechanisms for the association have been investigated in experimental conditions in paced human subjects (35;36) as well as in rat models (37;38) and where interventions were controlled for changes in arterial pressure (39). The effect has been suggested to be due to the viscoelastic properties of the arterial wall (40;41).

1.1.B “Active” mechanisms

Mechanisms of arterial stiffness associated with cellular and molecular processes have the potential for pharmacological interrogation of biochemical pathways. However, whereas the mechanical, structural and hemodynamic correlates of arterial stiffness that constitute the ‘passive’ mechanisms are well established (1), the biochemical pathways that constitute possible ‘active’ mechanisms and that lead to increased functional stiffness of the artery wall are not as well defined, although there is increasing interest across a range of fields in elucidating specific

molecules that may play a significant role (42). There is evidence that similar mechanisms are involved in vascular aging (27;43) and inflammation (44;45). Although specific evidence in humans is yet to be fully established, there is increasing evidence in experimental animals, comprised mainly of rodent models, of the modification of the extracelluar matrix through cellular, molecular, neurogenic and neuroendocrine pathways some of which may be potentiated by genetic mechanisms.

1.1.B.i Cellular Mechanisms

In the artery wall, the cellular mechanisms related to arterial stiffness are mediated by endothelial cells and smooth muscle cells. The description below does not relate to the effect of the cells *per se* to the wall stiffness, but rather the pathways associated with modification of the structural integrity of the arterial media, leading to modifications of functional stiffness of the arterial conduit.

1.1.B.i.a. Role of the endothelial cell in arterial stiffness

The interface of the endothelial cell layer with flowing blood predisposes the function of the endothelial cell to hemodynamic forces which have been shown to potentiate gene expression at the level of transcription (46). Hemodynamic forces are associated with modification of the artery wall through phenotypic alterations of endothelial and smooth muscle cells through complex mechanotransduction receptor mechanisms (47). Genetic expression has also been shown to be affected by the amount of pulsatility contributing to oscillatory shear. In cultured bovine aortic endothelial cells, the mRNA expression of Endothelin-1 (ET-1) and endothelial nitric oxide synthase (eNOS) has been shown to depend on both time and amplitude of mechanical force (48). These studies showed that compared to unidirectional shear, oscillatory shear stress combined with pressure upregulates transient expression of ET-1 while at the same time downregulating eNOS. Since arterial stiffness is associated with pulse pressure, this mechanism could constitute a potential positive feedback mechanism where downregulation of eNOS and upregulation of ET-1 could further increase wall stiffness, leading to increase in oscillatory sheer stress and so amplifying the effect of wall stiffness. Although limited, there is *in vitro* experimental evidence of this from cells cultured in tubes of different compliance where it

was demonstrated that increased wall stiffness is associated with reduced endothelial Akt-dependent eNOS phosphorylation (49).

The association of endothelial dependent reduction of nitric oxide (NO) and increased arterial stiffness has been demonstrated *in vivo* in the iliac artery of sheep (50) and humans (51). These experiments were conducted in a segment of vessel where the local effects of altered endothelial function could be quantified independent of effects of intra-arterial distending pressure. Similar experiments demonstrated the effects of ET-1 in potentiating elevation of larger artery stiffness which can be reversed by blockade of the ET(A) receptor (52). Natriuretic peptides have also been shown to affect local iliac artery stiffness in the sheep via the Natriuretic Peptide Receptor Type A (NPRA) receptor (53).

1.1.B.i.b. Role of the vascular smooth muscle cell in arterial stiffness

In addition to the important role of vascular smooth muscle in regulation of vascular tone affecting peripheral resistance, the contractile properties of the vascular smooth muscle cells have a measurable effect on mechanics of the arterial wall of large conduit arteries (41;54;55) with suggestions of regulation of energetics of viscous damping (56). However, there is a large body of literature spanning some 5 decades on the biology of smooth muscle cell phenotypic modulation, where the cell exists in a number of phenotypic states which depend on specific adaptive functional demands (57).

In relation to arterial stiffness, an important phenotypic change is the functional transdifferentiation leading to osteogenesis causing deposition of calcium in the media of the arterial wall (58). The increase in arterial calcium deposition has been related to decreased bone mineral density (59) and recent evidence has been obtained from the Baltimore Longitudinal Study of Aging that in women, there is an inverse relationship between arterial stiffness and cortical bone area, independent of age and blood pressure (60). The compounding effect of calcification is that facture of elastin fibers is associated with the signaling pathway for smooth muscle cell transdifferentiation (59) and that the downstream effect is elastocalcinosis resulting in increased wall stiffness (61;62).

In experimental investigations, increase in arterial stiffness mediated through calcification is associated with administration of vitamin D and nicotine (61;63). Vitamin D has also been found to be an independent correlate of arterial stiffness in patients with peripheral arterial disease (64). Elevated calcification is also a hallmark of chronic kidney disease in Lewis polycystic kidney (LPK) rat models. LPK rats showed a 6-8 fold increase in aortic calcification with 33% increase in aortic pulse wave velocity and 20% reduction in elastin density (65). Although vascular calcification is potentiated by phenotypic changes in the vascular smooth muscle cell, tissue transglutaminase 2 (TG2) has been shown to be necessary for programming chrono-osseous smooth muscle cell differentiation in response to increased bone morphogenic protein (66). Recent studies have also identified other pathways which affect smooth muscle cells to potentiate vascular calcification. Calpain-1 has been shown to regulate metalloproteinase 2 (MMP2) activity affecting age-related calcification and fibrosis (67). A mineralocorticoid receptor, usually thought to be present in the kidney, has recently been identified in vascular smooth muscle, suggesting a possible regulatory role in smooth muscle function (68).

1.1.B.ii Molecular Mechanisms

1.1.B.ii.a. Extracellular Matrix

Molecular mechanisms that alter the stiffness of the extracellular matrix (ECM) of the artery wall are connected with aging, involving changes in the structural proteins, elastin and collagen that are manifest as protein side-chain modification and intermolecular cross-linking (69). Whereas cross-linking involves enzymatic changes during developmental phases, aging involves non-enzymatic processes with glucose, leading to advanced glycation end-product (AGE) formation. In arteries, AGE formation in the ECM leads to increased stiffness, and it has been shown that non-enzymatic breaking of AGE crosslinks can improve arterial compliance and reduce pulse pressure in the elderly, as well as improving cardiac function (70;71). Recent studies question whether existing cross-links are actually cleaved by AGE breaking agents such as alagebrium (ALT-711), although these agents can act as inhibitors of metal-catalyzed AGEs (72). ECM remodeling is also modulated by the expression of MMPs due to effects of hemodynamics, oxidative stress and inflammation (73). The role of cardiotropin-1, a member of interleukin-6, in promoting fibrosis in the ECM leading to increased arterial stiffness has also recently been described (74).

1.1.B.ii.b. Protein post-translational modification: S-Nitrosylation

The process of S-nitrosylation involves post-translational modification mediated by nitric oxide (NO) through cyclic GMP independent pathways where a protein cysteine thiol undergoes covalent modification by an NO group and generates an S-nitrosothiol (SNO) (75).The S-nitrosylation process of the tissue transglutaminase protein type 2 (TG2) has been shown to be involved in the calcium-dependent TG2-mediated modification of the vascular extracellular matrix through formation of collagen cross-linking, affecting wall stiffness (76). The endothelial production of NO produces a cyclic redox-dependent S-nitrosylation and denitrosylation of TG2 (75). The reduced S-nitrosylation (and therefore increased denitrosylation) of TG2 that takes place with reduced production or bioavailability of NO (e.g. due to endothelial dysfunction) causes exteriorization of the protein to the extracellular space. Increased activity of matrix TG2 has been shown to be associated with increased aortic PWV in TG2 knockout mouse models (77). Studies in ageing rats and TG2 and eNOS knockout mice models have shown that reduction of bioavailability of NO as occurs with ageing, inflammation and endothelial dysfunction in general is associated with cellular mechanisms contributing to arterial stiffness (78) .

1.1.C Neurogenic Mechanisms

Investigations addressing the neurogenic influence of stiffness of large arteries through the effect of smooth muscle tone have been varied and have produced inconsistent results in terms of quantifying the intrinsic neurogenic effect on the smooth muscle as separate from the passive mechanical stretch effect due to concomitant pressure changes. Studies simulating the neurogenic effect by administration of neurotransmitter substances have demonstrated increased aortic PWV in anaesthetized dogs (79) and wall stiffness changes measured by pressure/diameter relations in conscious dogs (80) and vagotomised cats (81) Studies in rats have also been confined to measurement of specific sites (carotid and femoral arteries) and have not explicitly addressed the effect on the aortic trunk (82;83), in terms of functional stiffness determining pulse pressure. Recent studies in humans have shown an independent association between aortic PWV and muscle sympathetic nerve activity (84;85).

1.1.D Neuroendocrine Mechanisms

Early studies on cardiovascular effects of angiotensin converting enzyme (ACE) inhibition suggested a role of angiotensin II in cardiac and vascular remodeling independent of the passive effects of arterial pressure (86). The remodeling of the extracelleular matrix affecting arterial stiffness involves ACE inhibition preventing medial accumulation of collagen mediated by inhibition of angiotensin II through the AT1 receptor (87). Recent studies have associated the age-related changes in the arterial wall with angiotensin II signaling in complex pathways involving calpain-1, transforming growth factor-beta1, MMP 2 and 9, monocyte chemoattractant protein-1, NADPH-oxidase, and reactive oxygen species. Increased angiotensin II signaling has also been shown to induce the accumulation of collagen and advanced glycated end-products and elastin degradation (88).

In the LPK models of chronic kidney disease, it was shown that the increase in aortic stiffness was associated with a 6-fold increase in aortic calcium content (65). ACE inhibition by perindopril in the LPK rats
reduced the accumulation of aortic calcium during development as well as reducing the degree of elastin degradation and collagen content. In spontaneously hypertensive rats, early ACE inhibition for a brief period of only 4 weeks was associated with persistent reduction of isobaric wall stiffness (89).

Direct angiotensin receptor blockade (ARB) is associated with hemodynamic effects consistent with reduction of arterial stiffness and peripheral wave reflection (90). ARB also potentiated the reduction of arterial stiffness in combination with ACE inhibition in chronic disease (91). ARB is associated with blockade of the angiotensin II type 1 receptor. However, recent studies which have addressed the type 2 receptor have shown that chronic stimulation was associated with reduced aortic stiffening and lower collagen accumulation. This occurred without preventing hypertension in rats in which NO synthase was inhibited. The effects of type 2 receptor stimulation were additive to angiotensin II type 1 receptor blockade (92).

1.1.E *Genetic* Associations

The use of high density array single nucleotide polymorphism technology is enabling the identification of gene variants associated with markers of vascular function. Perusal of genome-wide association studies (GWAS) is uncovering groups of genes affecting NO pathways, MMPs, matrix elastin structure, endothelin receptors and inflammatory molecules (93). Specific associations with cfPWV have been found in a gene locus associated with gene enhancers related to increased stiffness as measured by PWV (94). Studies in specific populations, such as African Americans, have not yet yielded specific genes, although it is estimated that some 20% of the variance in arterial stiffness is inherited. However, in comparison to the genetic information obtained by GWAS techniques, studies of congenic strains of rats might have increased power for genetic identification. A recent study in a congenic strain of rats for the identification of quantitative trait loci for blood pressure has shown that the female blood pressure quantitative trait locus has been narrowed to a range of less than 7 Mbp in chromosome 5 (95). Although this was shown for systolic and diastolic pressure, it was not related to pulse pressure, hence it is not known if the association can be extended to arterial stiffness.

1.2 Arterial stiffness as manifestation of vascular aging

The most significant parameter that alters stiffness of conduit arteries is arterial aging (27;96). Arterial aging has a complex association with the overall burden of vascular disease (43), in different populations (97) and with associated cardiovascular risk (98). Indeed, recent reviews on the subject focus on the association between vascular aging and the broad spectrum of co-existing conditions associated with cardiovascular disease, such as hypertension, diabetes and metabolic syndrome and the management strategies of vascular aging (99).

1.2.A Potential arterial wall targets to prevent, delay or ameliorate age-associated increases in Arterial Stiffening and predominately systolic hypertension

Age-associated remodeling of the aortic wall arterial cell and matrix of both animals and humans involves a proinflammatory profile (100) (Figure 1.2). This profile features increased production of angiotensin II (Ang II) and increased vascular smooth muscle cell expression and secretion of downstream Ang II/AT_1, mineralocorticoid and endothelin receptor signaling molecules (Figure 1.3) e.g., MMPs, calpain-1 and monocyte chemoattractant protein (MCP-1), transforming growth

factor β1 (TGF-β1) NFκb, TNFα, iNOS, and VCAM. Activation of calpain-1, MMPs, TGF-β, and NADPH oxidase within the arterial wall is increased, and nitric oxide bioavailability is reduced (98;100-103). Invasive, proliferative and secretory capacities of early passage vascular smooth muscle cells (VSMC) isolated from the aged arterial wall are increased, and are linked to augmented Ang II signaling. This age-associated arterial proinflammatory secretory profile within the grossly appearing arterial wall and related structural/functional remodeling of cells and matrix is reproduced in young rats by chronic infusion of Ang II (104).

1.2.A.i Milk Fat Globule E8 (MFGE8)

A comprehensive quantitative proteomic study to analyze aortic proteins from young (8 months) and old (30 months) rats identified 50 proteins that significantly change in abundance with aging (105). One novel discovery was that milk fat globule E-8 (MFGE8; aka lactadherin or SED1) a pivotal relay element within the angiotensin II/MCP-1/VSMC invasion signaling cascade (Figures 1.3, 1.4), increases with age. Additional transcription and translation analyses in aortae of other mammalian species including humans demonstrated that MFGE8 mRNA and protein levels increase with aging of milk fat globule EGF-8 protein (MFGE8) also accumulates within the context of arterial wall inflammatory remodeling in hypertension, diabetes mellitus, or atherosclerosis (106). MFGE8 induces VSMC invasion and proliferation, both salient features of arterial inflammation (105;106) (Figures 1.3, 1.4). Chronic infusion of Ang II into young rats increases aortic MFGE8, MCP-1 and PCNA, an index of cellular proliferation, to levels in untreated old rats (104).

1.2.A.ii Aortic Amyloid Deposition

1.2.A.ii.a. *Characteristic Features and Pathophysiology of Amyloid Proteins*

Misfolding of extracellular protein to form amyloid deposits is a dynamic process, occurring in parallel with, or as an alternative to physiologic folding, generates insoluble protein aggregates that are deposited in tissues (107). The incidence of aortic amyloidosis in subjects over 40 years of age averaged 79% in 224 autopsy cases. The incidence prior to the 5th decade was 51% and

reached 95% by the 8th decade. The aortic media exhibited the majority of amyloid deposition, which consists of numerous minute deposits without a relationship to atheromata (108).

Amyloid has been defined, and specific amyloid types are defined, on the basis of its assembled protein fibril patterns. Initially, localized amyloid deposits, limited to certain organs or tissues, were regarded as innocent bystanders, or by-products of diseases, rather than having involvement in their pathogenesis. This view has changed radically during the last decade (109). Small amyloid deposits, or oligomeric preamyloid aggregates of specific amyloid fibril proteins, are now believed to be critical factors toxic cellular effects involved in the pathogenesis of common disorders, e.g. the amyloid b-peptide (Ab) in Alzheimer's disease and islet amyloid polypeptide (IAPP) in type II diabetes (109). Although mechanisms by which protein aggregates lead to cell injury and death are poorly understood, and fibrils are potential cytotoxins (110), *ß* sheet peptides (e.g., amyloid *ß*) are known to form ion channels in lipid bilayers possibly through aggregation, though the channel structure is not clear (111).

1.2.A.ii.b. Medin Amyloid (AMed)

Analysis of proteins extracted from amyloid-rich aortic media detected an amyloid protein called medin (112). Milk fat globule protein E8 is the precursor protein of medin amyloid, which becomes deposited in the aortic media in almost 100% of the Caucasian population over 50 years of age (113). Medin amyloid (AMed) is not restricted to the aorta and the temporal artery but also occurs in other arteries, mainly in the upper part of the body, including intracranial vessels (113). Medin amyloid deposits also contain its parent molecule, MFGE8. The medin fragment is 5.5 kDa and derives from the C2-like domain of MFGE8 (114). The C2-like domain has been shown to bind phosphatidylserine and the RGD motif binds $\alpha_v ß_3$ and $\alpha_v ß_5$ integrins (113-115). In vitro, medin forms amyloid-like fibrils and the last 18–19 medin amino acid residues are the aggregation-prone region (116). The two C-terminal phenylalanines may also favor amyloid formation (116).

In human aortae, medin amyloid co-localizes with elastic fibers of arteries (117) and is also associated with other elastic structures (113). There is some evidence to indicate that non-amyloid prefibrillar medin oligomeric aggregates may also be toxic to the surrounding cells. In vitro aggregated medin induces death of aortic smooth muscle cells, and cells incubated together with medin increased the production of MMP-2, i.e. a protease that degrades elastin and collagen (112).

Elastic fibers become arranged and anchored by a scaffold protein, fibulin-5. Fibulin-5$^{-/-}$ mice display aortic abnormalities due to disorganized and fragmented elastic fibers (118;119). Since MFGE8 promotes RGD motif-dependent cell adhesion(120) and binds to elastin, has been suggested that MFGE8, like fibulin-5 (118), is involved in organizing elastic fibers to cells (113). Both medin and MFGE8 bind to tropoelastin in a concentration-dependent fashion. It has been suggested that the medin domain mediates the MFGE8-tropoelastin interaction is a cell adhesion protein and its medin domain may connect smooth muscle cells to the elastic fibers of arteries (113). Given that both medin and MFGE8 interact with elastic fibers, elastin may be an important component in the formation of medin amyloid (113). It is believed medin may be a factor involved in the increased aortic stiffness that accompanies advancing age (113;117). Indeed, correlations between serum MFGE8 and PWV and cardiovascular risk factors have been observed older normal subjects and in elderly patients with type 2 diabetes mellitus (121).

Thus the age-associated increase in MFGE8 is a novel pivotal relay element within the angiotensin II/MCP-1/ERK/CDK4/VSMC invasion and proliferation signaling cascades, and medin amyloid production. Targeting of MFGE8 within this signaling axis pathway (Figure 1.4) is a potential novel therapy to reduce or delay age-associated arterial stiffening and inflammation that are also featured in diseases that become rampant at older ages, such as atherosclerosis and hypertension.

Central arterial fibrosis and calcification, features of age-associated arterial extracellular remodeling, are also linked to Ang II signaling. Angiotensin II induces MMP2 and calpain-1 expression and activity in the arterial wall (67;122) (Figures 1.3, 1.5). Cross-talk between these two proteases, calpain-1 and MMP2, leads to secretion of active MMP2, which modulates ECM remodeling via enhancing collagen production and facilitating vascular calcification (Figure 1.5). Thus, these molecules are new molecular candidates to retard age-associated ECM remodeling and its attendant risk for hypertension and atherosclerosis.

Age-associated central arterial remodeling involving arterial wall collagen deposition and elastin fragmentation are linked to the age-associated increase in arterial pressure. As noted in Figures 1.2 and 1.3, this arterial remodeling is linked to proinflammatory signaling, including transforming growth factor- β1, monocyte chemoattractant protein 1, and proendothelin 1, activated by extracellular matrix metalloproteinases (MMPs) and orchestrated, in part, by the transcriptional factor ets-1 (Figure 1.6).

Recent studies demonstrate that inhibition of MMP activation can decelerate the age-associated arterial proinflammation (123). Chronic administration of a broad-spectrum MMP inhibitor to 16-month–old rats for 8 months (Figure 9.8) resulted in (1) inhibition of the age-associated increases in aortic gelatinase and interstitial collagenase activity in situ; (2) preservation of the elastic fiber network integrity; (3) a reduction of collagen deposition; (4) a reduction of monocyte chemoattractant protein 1 and transforming growth factor- β1 activation; (5) a diminution in the activity of the profibrogenic signaling molecule SMAD-2/3 phosphorylation; (6) inhibition of proendothelin 1 activation; (7) downregulation of expression of ets-1; and (8) markedly blunted the expected age-associated increases in arterial pressure (Figure 1.7).
Collectively, these results indicate that MMP inhibition retards age-associated arterial proinflammatory signaling, and this is accompanied by preservation of intact elastin fibers, a reduction in collagen, and blunting of an age-associated increase in blood pressure.

A MEGACEPT EMERGES WITH THE REALIZATION THAT IN ARTERIES OF YOUNGER ANIMALS, IN RESPONSE TO EXPERIMENTAL INDUCTION OF HYPERTENSION OR EARLY ATHEROSCLEROSIS OR DIABETES, PARTS OF THIS PROINFLAMMATORY PROFILE WITHIN THE ARTERIAL WALL THAT HAVE BEEN STUDIED TO DATE ARE STRIKINGLY SIMILAR TO THE PROFILE THAT OCCURS WITH ADVANCING AGE (98) (Figure 1.8).

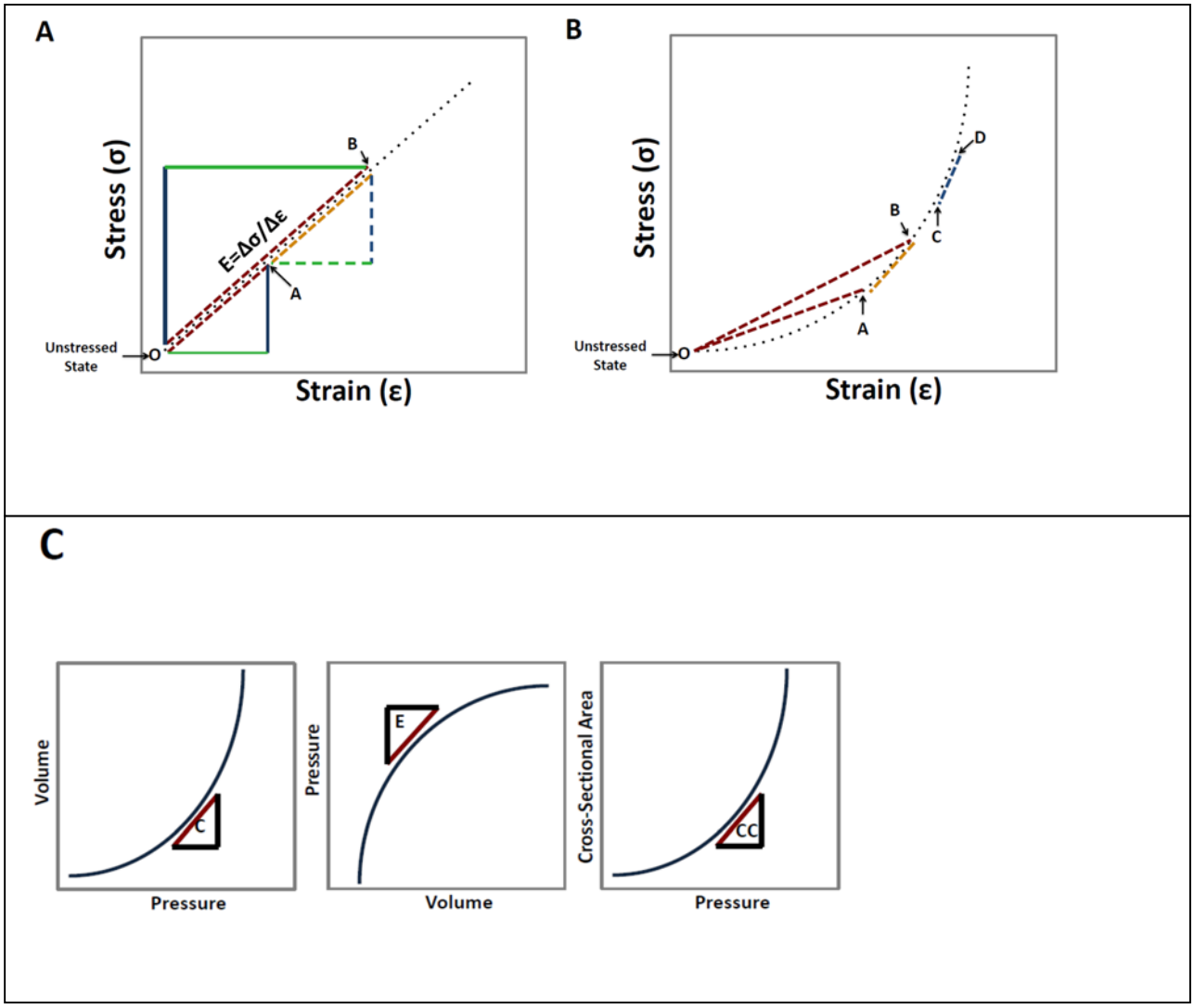

Figure 1.1

(A) Concept of Young's modulus for a Hookean (linear-elastic) material. O represents the unstressed state. The stress-straight relationship is represented by the dotted black line. Deformation from the O to point A is associated with a given stress (blue thin line) and strain (green thin line) for which Young's modulus can be computed as the slope of the stress / strain (red dashed line). Similarly, deformation from the O to point B is associated with a change in stress (blue thick line) and strain (green thick line) for which Young's modulus can be computed as the slope of stress / strain (red dashed line). Note than both computations use the change from the unstressed state O. For Hookean materials, Young's modulus is identical (constant) regardless of which point (A, B or any other) is used to compute the stress/strain relationship. The incremental change in stress could be computed from point A to B, without using the unstressed state. The incremental change in stress (thin dashed blue line) and strain (dashed green line) would then provide an incremental elastic modulus (Einc, also called incremental Young's elastic modulus), which is the slope of the two (orange dashed line). Note that for linear-elastic stress-strain relations, the incremental elastic modulus is identical to the elastic modulus computed from the unstressed state.

(B) Concept of incremental elastic modulus for a non-Hookean material. O represents the unstressed state. The curved stress-straight relationship is represented by the dotted black line. Deformation from the O to point A is associated with a given Young's modulus, which is different from the Young's modulus associated

with deformation from point O to point B. The *incremental* elastic modulus (Einc, also called Young's incremental elastic modulus) can be computed as the "local" slope of stress / strain (orange dashed line) is also different and better reflects the "operating" stiffness. Within this narrow range of stress and strain, non-linearity is small and a linear slope is quasi representative of the stress strain relation. Note that the incremental elastic modulus also varies according to the operating range of stress and strain. For example, the A->B incremental modulus (orange dashed line) is different than the C->D incremental modulus (blue dashed line).

(C) Concept of compliance, elastance and (cross-sectional) compliance coefficient. These measures represent the local slope of the pressure-volume, volume-pressure or cross-sectional area/pressure relation, respectively.

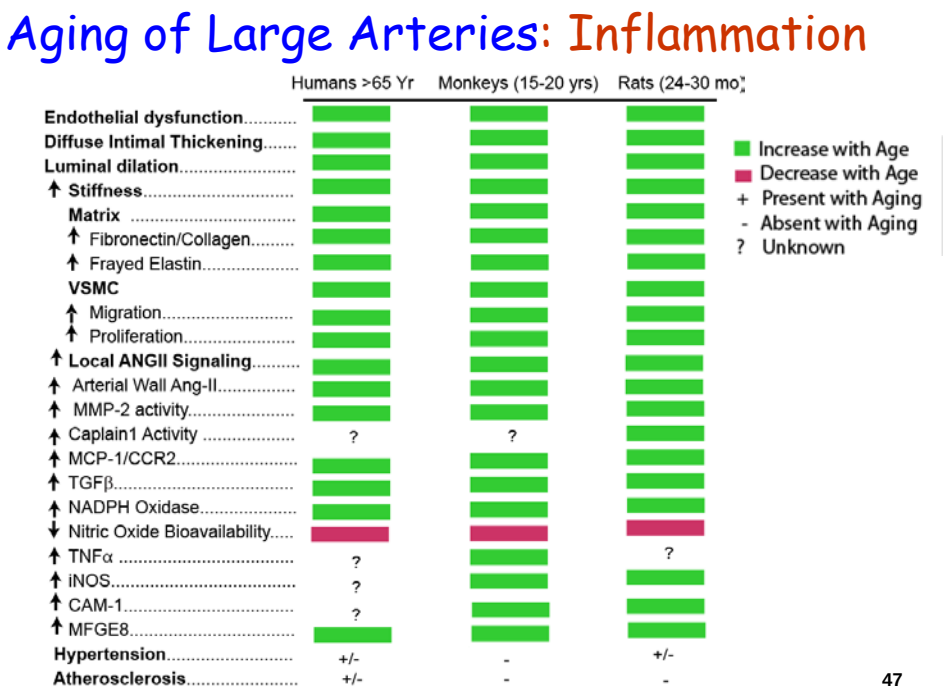

Figure 1.2 Inflammation and aging of arteries comparing primates with rodents

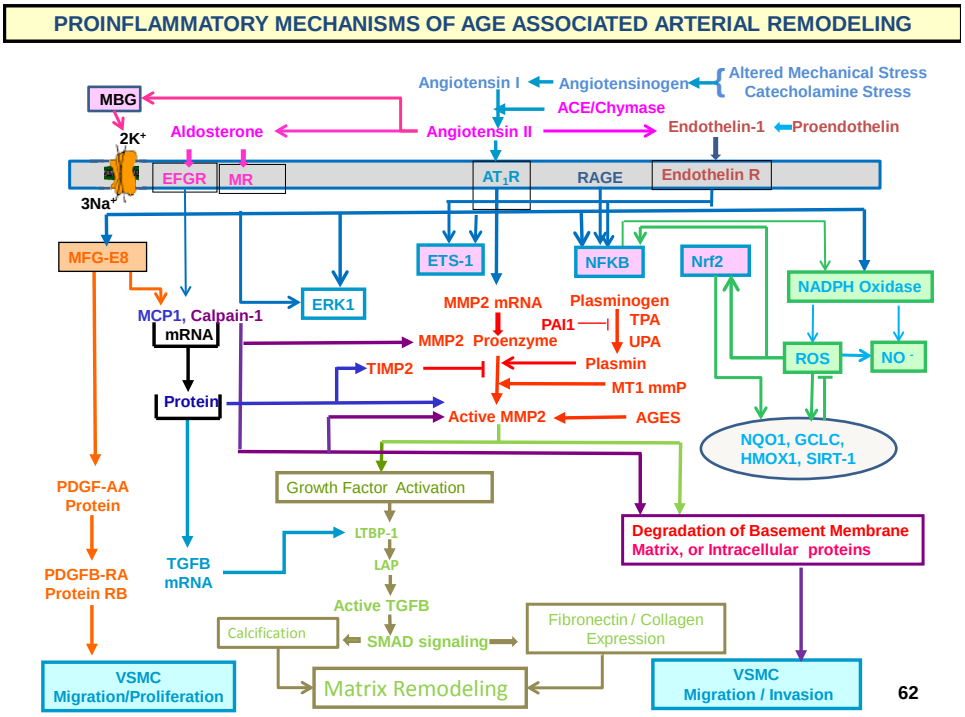

Figure 1.3 Proinflammatory mechanisms of age-associated arterial remodeling, see text and glossary of abbreviations to expand abbreviations in this figure.

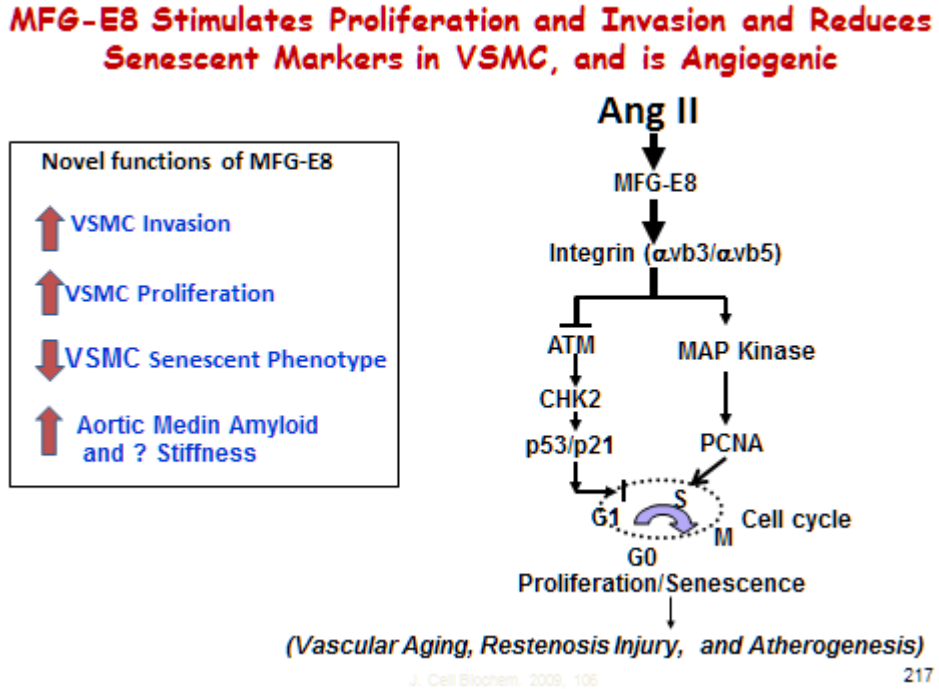

Figure 1.4 MFGE8 and Vascular Smooth Muscle Cell Markers

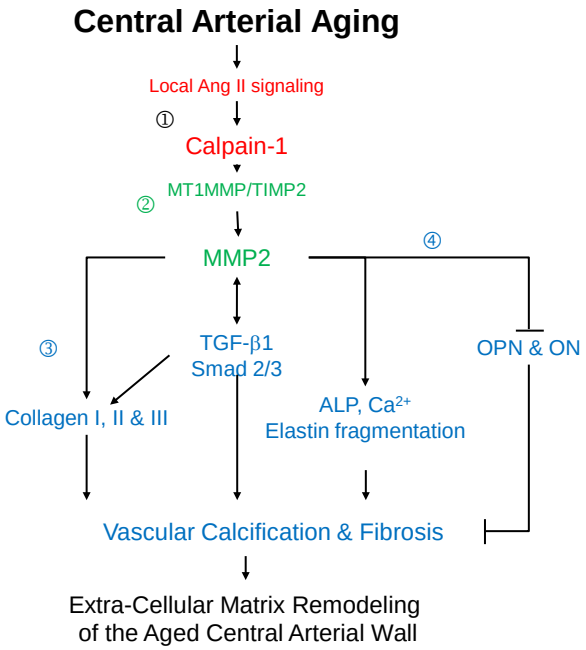

Figure 1.5 Mechanisms of central arterial aging that focus on the role of matrix metalloproteinase

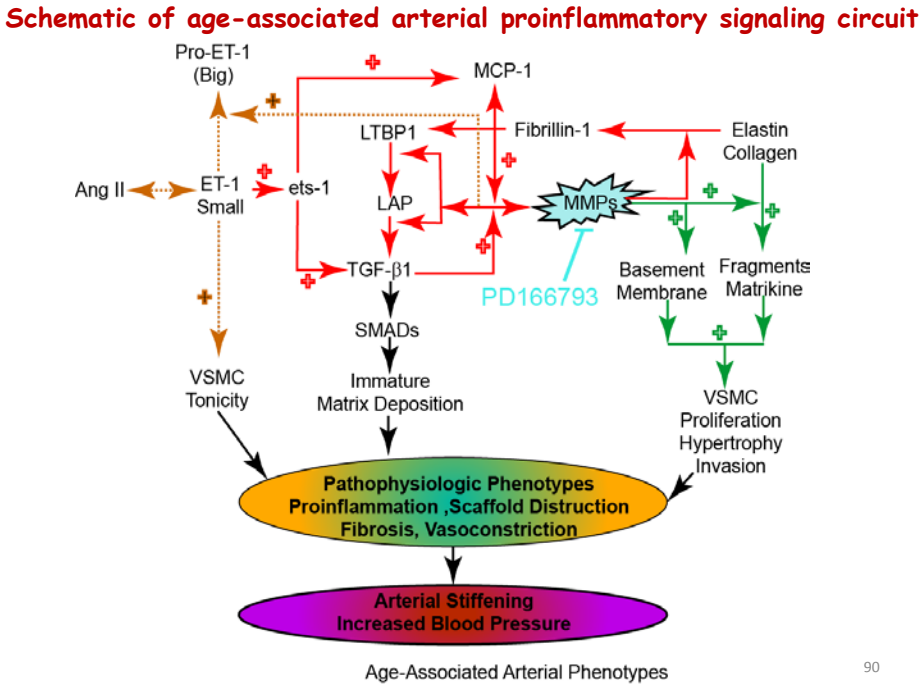

Fig. 1.6 Age-associated arterial proinflammatory signaling circuit

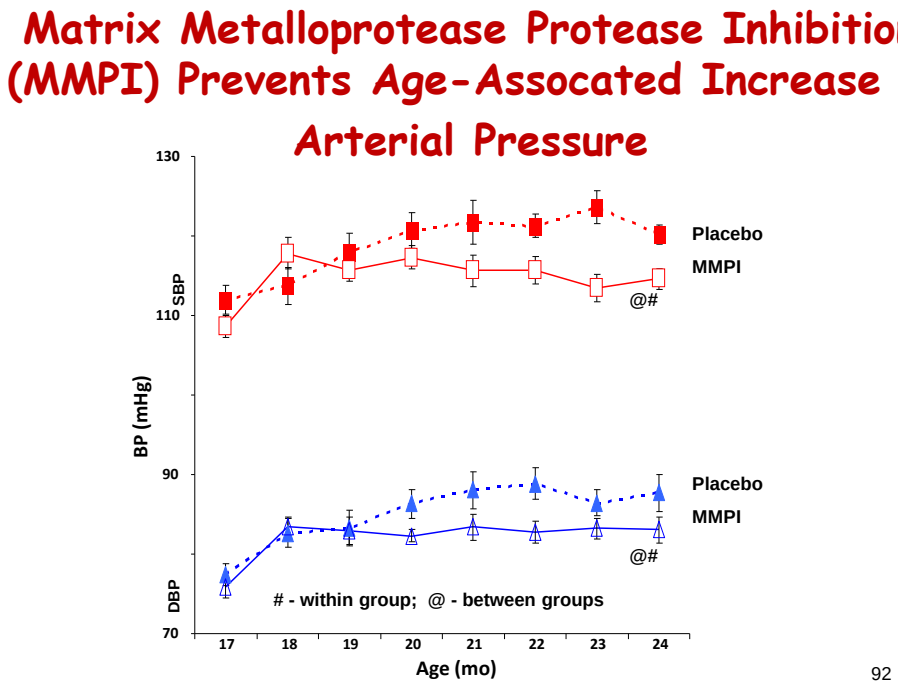

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Figure 1.7 Age-associated increase in arterial pressure and MMPI inhibition

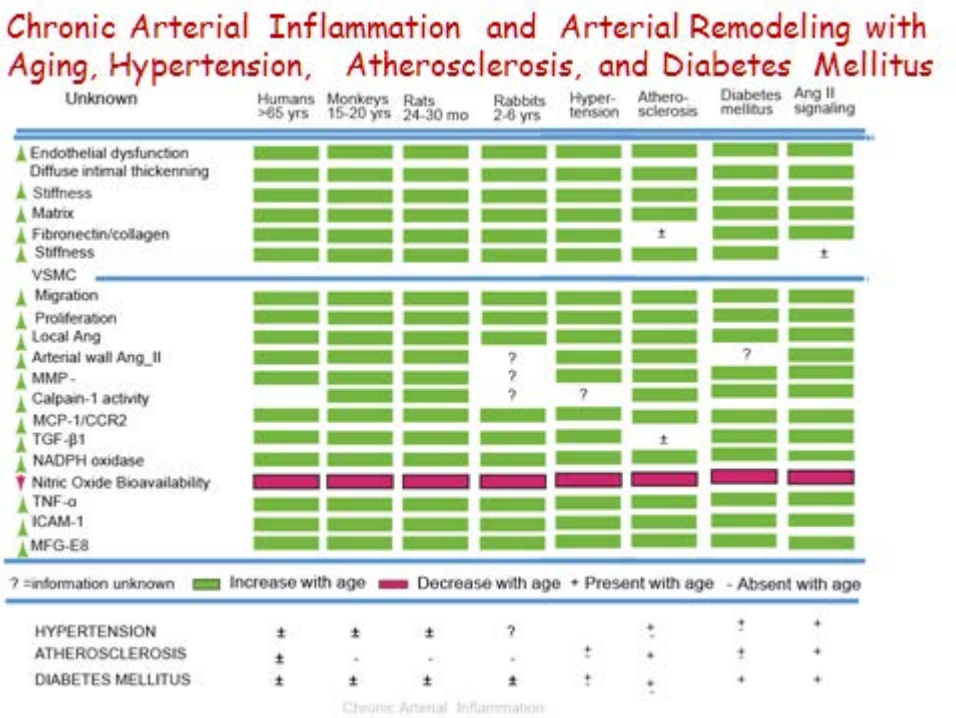

Figure 1.8 Chronic arterial inflammation

SECTION 2: Devices used to measure arterial stiffness

Authors: Raymond R. Townsend, Gary F. Mitchell, Thomas Weber

Before delving into the practical measurement of arterial PWV it is important to note that there are a variety of misunderstandings and limitations in this important and emerging area of clinical medicine that are often not appreciated. Estimating arterial stiffness is a challenge, given the complexity in the arterial system and the segment(s) measured. At any selected point in the arterial circulation, the elastic properties of the arterial wall are nonlinear and, thus, difficult to model simplistically. The physical properties of the arterial wall vary in different arterial segments, explaining the marked discrepancies in pulse wave velocities noted (for example) in the proximal aorta (which has low PWV) compared with the brachial artery (which has much higher PWV). Moreover, the arterial PWV depends substantially on the mean arterial pressure and increases progressively at higher MAP values, making it important to compare PWV within or between individuals at isobaric conditions (124).

It is possible to measure PWV invasively with indwelling catheters. This is often the approach in animal models and some human studies performed in the catheterization laboratory or the operating theater. Although this technique can be of value for the validation of non-invasive devices (see below), we will not address further these techniques as they are beyond the intent of this manuscript, and infrequently done in humans since the focus is on human measurement as it is used in clinical research and ultimately, in clinical practice.

The most frequent site used to measure pulse wave velocity is the aorta (125). Because a velocity is simply a function of distance and time, most approaches to PWV measurement input a distance measurement (or assume distance based on a nomogram for a particular population). A common approach is the measurement from the suprasternal notch to the site where a carotid pulse can be felt (often around 80-100 millimeters) and the suprasternal notch to the place where the femoral pulse can be felt (often around 500-600 millimeters). Because the pulse wave travels from the aorta to the carotid site simultaneously with pulse wave travel across the rest of the aortic arch the carotid distance is subtracted from the suprasternal notch-to-femoral distance. For

example if a suprasternal notch-to-carotid measurement was 95 mm and suprasternal notch-to-femoral was 575 mm, the net distance traveled would be: 575mm-95mm = 480mm.

Measurement of pulse wave speed requires a means to detect pulse wave arrival at the two points. The specifics of these measurements are outlined later in this section, but a shared characteristic of all techniques is the need to be able to clearly mark the onset of the pulse wave at that site. In general, the foot of the waveform, just before the upslope of the waveform, is chosen as it is least affected by wave reflections, and has proven reliable in the various methods used (1). Whether using a flow or a pressure wave, it is important to measure similar points in the two waveforms so that the time delay can be estimated.

Methodologies

Measurements of PWV are undertaken using several methodologies. These fall into four main categories:

- Devices that use a probe or tonometer to record the pulse wave using a transducer
- Devices using cuffs placed around the limbs or the neck that record pulse wave arrival oscillometrically
- Ultrasound approaches
- Magnetic resonance imaging (MRI)-based approaches

Devices using a probe or a tonometer to measure PWV

The SphygmoCor ® device (Atcormedical, Australia) uses a Millar tonometer which is placed at any two places where a pulse is detectable to record PWV. There is only one tonometer attached to the unit so PWV measurements require two separate sets of readings, typically 10 seconds in duration, to be taken. The subject's blood pressure is entered to calibrate the waveform, and proximal followed by distal distance measurements (for example suprasternal notch to carotid artery palpation site, and suprasternal notch to femoral artery palpation site) are entered, in millimeters, into the software. Since they are sequential, not parallel measurements, a method to time the appearance of the pulse wave at the measurement site is necessary. This is done by using a standard limb lead II electrocardiogram (EKG) tracing. The time (measured in milliseconds) elapsing from the tip of the QRS in lead II to the onset of the "foot" of the pulse

wave is measured over 10 seconds, and averaged for that site. Then the procedure is repeated for the second site. Since velocity is a distance divided by time, the software calculates the travel distance (distal – proximal measurements) and divides this by the difference in the averaged distal minus the averaged proximal time measurements.

The SphygmoCor device has been used in Anglo-Cardiff Collaborative Study of arterial stiffness (126) and the CRIC study of chronic kidney disease (127), as well as other cohorts and intervention studies. Newer versions of this device (XCEL ®) use a cuff and tonometer system to record simultaneous pressure waves (128).

Published reproducibility of the PWV with the SphygmoCor is good (129). In this section, unless otherwise stated, reproducibility of a technique was established using Bland-Altman Plot analyses (130).

The Complior ® (ALAM Medical, France) measures the PWV from distension sensors that register pulse waves in the cuffs, and in the special neck sensing unit used. Up to 3 arterial segments can be assessed simultaneously, and typically the neck, the upper arm and the upper leg are used from which carotid-radial and carotid-femoral PWV are determined. The Complior software provides an on-line pulse wave recording and automatic calculation of the pulse wave velocity(131).When the operator determines that the pulse waveforms seen in real time on the computer screen are of good quality the system stops acquiring waveform data and calculates the time delay between the two waveforms of interest (such as carotid and femoral) using internal filters that remove artifacts from the waveforms. The operator has entered a distance measure into the software and the system uses 10 heartbeats to calculate an average time delay (in milliseconds) which is then entered into the standard calculation.

This device has been used extensively in epidemiologic studies in Europe and formed much of the database, particularly in dialysis patients, showing the significant and independent contribution of aortic PWV to cardiovascular (CV) morbidity and mortality (132-134) as well as contributing much of the data used in the European Society of Hypertension (ESH) consensus statement (135).

Published reproducibility of the PWV with the Complior is good (136).

The PulsePen (DiaTecne, Italy) uses an ECG signal and a hand held tonometer (similar to the SphygmoCor) to perform carotid-femoral pulse wave velocity measures. The PulsePen has been used in the Predictive Value of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population (PARTAGE) study conducted in elderly patients in France and Italy (137). Published reproducibility of the PulsePen is good (138).

Cardiovascular Engineering, Inc., (Boston, MA) uses a custom device to measure PWV using 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 suprasternal notch. The EKG 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 (139) and Reykjavik Studies (140), as well as other cohorts and intervention trials. Reproducibility of the PWV by this method is reportedly good (Gary Mitchell, personal communication).

Devices using cuffs placed around the limbs or the neck that record pulse wave arrival oscillometrically

One oscillometric device, particularly popular in Asia, is the VP1000 ® (Omron Healthcare, Japan). This device places four cuffs on both arms and both ankles and performs a brachial-ankle pulse wave velocity (baPWV). It also provides an ankle-brachial index (ratio of systolic pressure in the ankle compared with that of the brachial artery; a marker of peripheral arterial disease when this ratio is < 0.9). The newer model (VP2000) has additional probes which can be secured in place (with straps) that detect carotid (CAP) and femoral (FAP) pulses simultaneously (i.e. both probes capture the same pulsewave) by tonometry. EKG leads are attached, as is a phonocardiographic microphone (whether the measurements are being done by oscillometry or tonometry). The subject's age, height and gender are entered into the software and the distance estimate is calculated using statistical norms (based on Japanese individuals).

The Omron device has been used in prospective observational studies independently predicting loss of kidney function (141), cardiovascular disease (142), and all cause death (143)

Published reproducibility of the PWV with the VP1000 is good (144).

The Mobil-O-Graph ® (IEM, Germany) uses a cuff based method to measure brachial blood pressure (causal and 24 hour), to estimate central aortic pressures by pulse wave analysis (PWA), and to estimate carotid-femoral PWV (145). The Mobil-O-Graph 24h PWA ABPM device (IEM, Stolberg, Germany) uses a proprietary algorithm to obtain conventional brachial blood pressure readings after which the brachial cuff is inflated to the diastolic blood pressure level and held constant for about10 seconds to record the pulse waves. Subsequently, central pressure curves are obtained using a transfer function. To estimate aortic PWV, several parameters from pulsewave analysis, along with wave separation analysis are combined in a proprietary mathematical model incorporating age, central pressure, and aortic characteristic impedance(146). The Mobil-O-Graph aortic PWV values have been validated by direct intra-arterial measurement in the catheterization laboratory (147).
Reproducibility of the Mobil-O-Graph is also good (148).

The VaSera (Fukuda Denshi, Japan) uses cuffs on all four limbs and gates the timing for the pulse wave arrival at the ankle relative to the heart using phonocardiography through a small microphone taped onto the chest (149). In addition to cardiac-ankle pulse wave velocity (reported as a cardio-ankle vascular index; 'CAVI') it also provides an ankle-brachial index. This device has been used mainly in Japan for longitudinal studies of dialysis patients (150) as well as in community studies of cognitive decline (151).
Reproducibility of the Vasera is good (152).

Ultrasound approaches

Unlike tonometric or mechanotransducer methodologies which were developed for the dedicated purpose of measuring pressure wave travel, ultrasonographic techniques used to measure PWV leverage technology that is useful for many imaging purposes, and are not restricted to a dedicated service. Many ultrasound devices have been used for such purposes and the following descriptions are more general, and not as device specific, as in prior sections.

Ultrasonographic approaches have been used to measure PWV either at a particular location, or in a region of the arterial circulation. When used in a single location, for example the brachial artery, the ultrasound captures the changes in arterial diameter and area and uses the Moens-

Korteweg equation (153) where 'c' is the PWV. In this equation E_{inc} is the elastic modulus calculated in the middle panel. To derive the compliance term (Change in area for change in pressure) the formula on the right panel is used. The ultrasound is able to provide the change in area ('dA' which is due to the cardiac cycle –systolic and diastole), and (continuing with the brachial artery as an example) the systolic – diastolic pressure (i.e. the pulse pressure) is entered for the change in pressure ('dP'). In the numerator of the middle panel equation the πro^3 ('ro'=radius) term can be separated into $\pi r^2 * r$ (or area * r). Since 2*r is diameter, the numerator for the middle panel equation becomes $Area_0$*$diameter_0$. Substituting into the denominator from the right panel equation we now have $E_{inc} = Area_0*diameter_0/[dA/dP]*h_0$ (where h_0 is the vessel wall thickness). Inserting this into the left panel, the h_0 cancels out, the d_0 cancels out, the values for $Area_0$ and dA are entered from the ultrasound data, the local pulse pressure is entered for the dP, and a value for ρ (typically 1.05 gm/cm^3) is entered and the velocity calculated. This usage of ultrasound is uncommon, and limited by the challenges in accurately assessing the change in area (dA) of the aorta.

$$c = \sqrt{(Einc * ho)}/(\rho * do)$$

$$Einc = 2 * \pi * ro3/CA*ho$$

$$CA = dA/dp$$

Doppler ultrasound using two microphones, simultaneously, has been used to measure regional (usually aortic) PWV in several studies (154). Typically one microphone is clamped to the left side of the neck to insonate the site of the left subclavian artery and the second microphone is secured on the abdomen insonating the abdominal aorta above the bifurcation. Distance is measured from the suprasternal notch to the location of the second microphone. This can be challenging since the angle of insonation makes it difficult to reliably determine where the abdominal aorta is being insonated 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, and not uncommonly 1-2 minutes of recordings are done (155).
In some cohorts, Doppler signals were acquired in sequence using a single microphone, and insonating the right common carotid artery and the right femoral artery (156). These techniques have shown independent predictive value for cardiovascular outcomes, and death, in longitudinal studies of diabetics (155), the healthy elderly (157) and a general population (156).
Ultrasound is also used to assess local (cross sectional) distensibility of vessels such as the carotid artery. B-mode ultrasound, video analysis and echo-tracking methodologies are common approaches used (135;158). Section 6 (below) has an expanded discussion of this aspect and device comparisons in Table 6.4.
Published reproducibility of ultrasound-based PWV is good (159;160)

Magnetic resonance imaging (MRI)-based approaches

There are several magnetic resonance imaging (MRI) methods to assess arterial stiffness. Phase-contrast MRI (PC-MRI) can be used to assess blood flow. This technique relies on the fact that, when 2 opposing magnetic gradient pulses are applied to static nuclei aligned in a magnetic field, the effects of the two pulses on their nuclear spin cancel each other out, but if a particle moves in the time between the pulses, a shift in the phase of the nuclear spins within the moving particle is accumulated, which is proportional to the velocity of movement along the gradient's direction (161). PC-MRI can be used to acquire blood flow velocity maps along any given anatomical 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 pulse wave velocity. 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 (VENC), 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 VENC should be tailored to individual measurements, a VENC of 130-150 cm/sec allows for an 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 in-homogeneities of the magnetic field environment (short-term eddy currents) (161;162), signal loss due to turbulent flow, partial volume averaging due to limited spatial resolution, signal misregistration due to 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 (163-166).

A second approach to measure arterial stiffness with MRI involves the assessment of arterial distension, 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 for automatic segmentation of aortic lumen throughout the cardiac cycle. Such approaches can be used for the assessment of 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, since available tonometry systems are not MRI-compatible. Irrespective of the approach used, it is critical to include an accurate measurement of blood pressure at the time of stiffness measurement because the mean arterial pressure is an important determinant of stiffness (see section 7 and recommendation 7.1).
Good reproducibility of PWV by phase-contrast MRI has been reported, with intraclass correlation coefficients ~0.90 (167).

Other approaches to measuring arterial stiffness

The HDI Profiler ® (Egan, MN) is a device which uses a radial artery waveform acquired by tonometry and calibrated by a brachial blood pressure to derive indices of arterial stiffness. Several indices can be obtained based on pressure measurements at a single site, which may be variably influenced by arterial mechanical properties, cardiac function and other hemodynamic phenomena. Analyses of pulse wave morphology can provide various indices which may or may not directly relate to arterial stiffness. Some authors (168-172) have proposed the application of a 4-element Windkessel model of the arterial tree using the diastolic pressure decay from a radial pressure waveform as an input. The HDI device applies such modeling in order to derive 2 indices (C1 and C2), which have been proposed to represent large and small artery elasticity, respectively (168-172). Associations between indices derived from this model and cardiovascular risk factors (such as aging, hypertension or diabetes), incident hypertension (173) and renal function decline (174) have been reported. However, there are important limitations to this approach, including: (1) The lack of a measured cardiac output (a critical input to the model), which is rather derived from age and body surface area and demonstrates a poor correlation with measured cardiac output (175); (2) The fact that parameters obtained with this method are not independent of the measurement location (175;176) challenges basic assumptions inherent to the model. Whereas a large number of studies in multiple cohorts have unquestionably demonstrated that large artery stiffness is a strong predictor of cardiovascular risk, the C1 index derived from this method (proposed to represent large artery elasticity) failed to predict cardiovascular risk in the Multiethnic Study of Atherosclerosis (177). C2 has been named “distal compliance” “oscillatory compliance” “reflective compliance” and more commonly “small artery elasticity”. Whereas C2 has been shown to predict cardiovascular events (177;178), there is no evidence that this index actually measures the elasticity or compliance of small arteries. The use of multiple names for this index illustrates the lack of a straightforward physical interpretation of this parameter. Given the unclear physiologic meaning of some model parameters, we recommend against the use of descriptive names (such as “small artery elasticity”) in favor of less descriptive terms (such as “C2”). Given the available epidemiologic and clinical data, there is a need for a better characterization of the physiologic determinants of C2.

The ambulatory arterial stiffness index (AASI), computed as one minus the slope of the linear regression line between systolic and diastolic blood pressure during 24-hour ambulatory brachial

blood pressure recordings, despite its designation as a stiffness index, is not a direct measurement of arterial stiffness (179;180). Physiologic principles suggest that this index is likely to be influenced by other factors, such as heart rate, stroke volume and vasomotor tone, as well as their circadian changes (all of which are expected to affect the relationship between systolic and diastolic blood pressure at any given level of large artery stiffness in a 24-hour recording). Westerhof *et al* established, from a theoretical point of view, the dependency of AASI on heart rate and systemic vascular resistance and its role as an indicator of ventricular-arterial coupling (by which the heart rate is "coupled" with the rate of diastolic pressure decay to maintain systolic and diastolic pressures within adequate ranges), rather than an index of arterial stiffness (181). Kips et al showed that the confounding effect of heart rate and vascular resistance constitute an important limitation of AASI as an index of arterial stiffness (180). AASI has also been shown to be influenced by the degree of nocturnal blood pressure fall (179). Therefore, the value of AASI as a surrogate of arterial stiffness is unclear. Indeed, only a relatively weak correlation was reported between AASI and aortic PWV in one study, which did not persist after adjustment for age (179). It is important to note that the fact that although AASI is not a direct measure of arterial stiffness, that does not necessarily imply that it is not a useful marker of cardiovascular risk. AASI has been shown to independently predict cardiovascular mortality (182;183) and stroke(184) in large prospective studies.

Limitations in methodologies

In all carotid-femoral methods there is an issue of how distance of travel is measured (185) [see sections 6 and 7]. In addition, PWV changes as the waveform travels progressively further from the heart in the aorta; thus the PWV value obtained represents a spatial average.

Sequential methods where there is a single microphone, tonometer or mechanotransducer measures the PWV transit time using different heartbeats, and reconstruct the delay using the ECG as a fiducial point. Therefore, the methods are sensitive to alterations in heart rate and the pre-ejection period, which may alter the relation between the R wave and the foot of the proximal and distal pressure waveforms.

MRI is limited by low temporal resolution, high cost, limited accessibility to MRI-scanners in many centers, less widespread available expertise and incompatibility with various ferromagnetic objects. In claustrophobic subjects, MRI may not be feasible and anxiolytics/sedatives,

commonly used clinically to overcome claustrophobia, may have vasoactive effects, influencing arterial measurements.

SECTION 3: Importance of Arterial Stiffness

Authors: Gary F. Mitchell, John Cockcroft, Carmel McEniery

Background

Over the past two decades, arterial stiffness has emerged as a major new risk factor for several common adverse health outcomes, including cardiovascular disease(132;133;139;157;186-190), stroke(187), mild cognitive impairment and dementia(140;191-197), retinal disease (198;199), and kidney disease(127;200-203). Arterial stiffness increases variably and nonlinearly with advancing age, with modest change in the first 5 decades of life and markedly accelerated change thereafter (204-206). The prevalence of increased aortic stiffness, assessed as cfPWV greater than 12 m/s, is a few percent prior to 50 years of age but nearly 70% after 70 years of age (207). Arterial stiffness is associated with atherosclerosis, although the association is not a strong one (208). The pathophysiology of arterial stiffening differs from that of atherosclerosis and is associated with different risk factors (209;210). Once established, arterial stiffening is associated with various severe non-atherosclerotic consequences (211;212). 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 (213;214). The combination of a high prevalence of increased arterial stiffness in older people, higher risk for adverse outcomes in the presence of increased stiffness and aging of the population forebodes emergence of an epidemic of arterial stiffness-related disease over the next decades unless specific interventions are implemented that prevent or curtail age-related arterial stiffening.

Arterial stiffness and cardiovascular disease (CVD) risk assessment

The prognostic value of stiffness measures for incident cardiovascular disease has been well documented in numerous community-based and disease-based cohorts by various investigators in many countries throughout the Americas, Europe and Asia. Conventional brachial pulse pressure, a widely available if somewhat nonspecific measure of aortic stiffness in older individuals, has been related to incident cardiovascular disease in thousands of publications, involving numerous large, independent cohorts (215-230). cfPWV, which is currently considered to be the gold standard measure of aortic stiffness, predicts major cardiovascular

disease events in models that consider standard risk factors including concurrent blood pressure and pulse pressure (132;133;139;155-157;186-189;231-237). Consideration of cfPWV reclassifies risk in individuals at intermediate risk for CVD, suggesting that consideration of cfPWV provides novel risk information beyond that provided by standard risk factors (139). The added benefit of cfPWV may be a manifestation of the relatively modest relation between cfPWV and standard risk factors other than age (209). A genome-wide association study has identified a locus on chromosome 14 that is associated with increased cfPWV and has demonstrated that the locus is also associated with a proportional increase in risk for a major CVD event, suggesting that cfPWV is a risk factor for CVD rather than just a marker of risk (94). The relatively weak associations between standard risk factors and cfPWV underscore the need to elucidate mechanisms associated with aortic stiffening in order to identify novel targets for interventions. A recent meta-analysis of studies that have evaluated relations between cfPWV and major CVD events has shown a consistent, moderate relation between cfPWV and level of risk in models that adjusted for standard CVD risk factors (190).

Arterial stiffness and the heart

Excessive arterial stiffness represents a compound insult on the heart. Aortic stiffening increases systolic load on the left ventricle, which contributes to ventricular hypertrophy and reduced mechanical efficiency, leading to an increase in myocardial oxygen demand (238;239). Stiffening is also associated with widening of pulse pressure and a reduction in mean diastolic pressure relative to mean systolic pressure. Since coronary flow is normally highest in diastole, diastolic coronary perfusion falls and demand increases as the aorta stiffens and pulse pressure widens (240). Arterial stiffening may be associated with diastolic dysfunction (241;242), which increases cardiac filling pressure and further limits coronary perfusion. Finally, arterial stiffness is associated with atherosclerosis (243-246), which may further impair ventricular perfusion, possibly leading to catastrophic reductions in ventricular function during ischemia (240). Arterial stiffness is associated with diastolic dysfunction and diastolic heart failure due to direct effects of abnormal load and loading sequence on myocyte contraction and relaxation and indirectly through ventricular hypertrophy (242;247-251). 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 (252). Arterial stiffness is associated with increased

risk for incident heart failure (223) and is increased in patients with established heart failure whether left ventricular function is preserved or impaired (253-255). The added load imposed on the heart by a stiff aorta may contribute to development of heart failure directly through effects on ventricular structure and function or indirectly by promoting atherosclerotic disease, myocardial infarction and secondary heart failure. Alternatively, neurohumoral activation in patients with heart failure may contribute to fibrosis and stiffening of the aorta, contributing to the observed association and creating the potential for a vicious cycle (256;257).

Aortic stiffness and peripheral vascular function

Effects of excessive pressure and flow pulsatility. In young, healthy adults, the aorta is highly compliant and first generation muscular arteries are relatively stiff. The abrupt transition from the compliant (low impedance) aorta to the stiff (high impedance) muscular arteries creates impedance mismatch. When a traveling wave encounters such a discontinuity, a portion of the pulsatile energy stored in that wave is reflected and therefore is not transmitted into the distal vasculature. Wave reflection at the junction between the normally compliant aorta and relatively stiff muscular arteries may represent a protective mechanism that limits transmission of excessive pulsatility into the microcirculation (258). The magnitude of the reflection coefficient at such a boundary depends on the degree of impedance mismatch between proximal and distal vessels, with a greater difference in impedance producing a larger reflection (140;259). A disproportionate increase in aortic impedance with little change or a decrease in muscular artery impedance with advancing age and in the presence of various vascular risk factors leads to progressive impedance matching between aorta and peripheral arteries. Impedance matching reduces the reflection coefficient and hence 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 (140;205;206).

Resistance vessel remodeling and impaired reactivity. Prior studies have shown that increased aortic stiffness and excessive pressure pulsatility are associated with increased resting microvascular resistance and markedly impaired reactivity in response to ischemic stress in the forearm (260). Resistance vessel remodeling, as assessed by the media-lumen ratio, is more closely related to pulse pressure than mean pressure, suggesting that anatomical constraints may contribute to limited reactivity in remodeled vascular beds (261-264). Indeed, a recent study

demonstrated a significant relationship between aortic PWV and media lumen ratio in a cohort of hypertensive subjects after adjustment for age and blood pressure (265). Dynamic tone in small arteries is also affected by pressure pulsatility (266-269). As a result, vascular resistance in autoregulated organs such as the kidney and brain may depend on pulse pressure as well as mean arterial pressure. If resistance vessel tone increases in response to pulse pressure at a constant level of mean pressure, flow will fall as resistance increases. Hence, alterations in the relation between mean and pulse pressure could lead to dissociation between mean pressure and resistance and interfere with autoregulation of flow. Beyond midlife, pulse pressure increases rapidly as mean pressure remains constant or falls, potentially putting autoregulated organs at risk for relative ischemia.

Labile blood pressure and transient ischemia. High aortic stiffness is associated with increased blood pressure lability (270-272). A stiffened vasculature is less able to buffer short term alterations in flow. Increased aortic stiffness is also associated with impaired baroreceptor sensitivity (271;273-275). Together, these limitations may result in potentially marked alterations in blood pressure as cardiac output changes during normal daily activities, such as changes in posture and physical exertion (276). The concordantly unfavorable combination of impaired microvascular reactivity and excessive blood pressure lability in an individual with a stiffened aorta may contribute to insidious damage to vascular beds and chronic microvascular ischemia throughout the body, leading to progressive target organ damage that eventually manifests as symptomatic disease(258;277).

Arterial stiffness (arteriosclerosis) is associated with atherosclerosis, although the association is not a strong one and the two 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 stasis or flow reversal during diastole (211). Arteriosclerosis also has important implications for structure and function of the microcirculation.

Arterial stiffness and the brain and eyes

Relations between aortic stiffness and structural lesions in the brain. High flow organs such as the brain and eye are particularly sensitive to excessive pressure and flow pulsatility (278). High

local blood flow is associated with low microvascular impedance, which facilitates penetration of excessive pulsatile energy into the microvascular bed (140). Aortic stiffening is associated with microcirculatory remodeling that may serve to limit capillary exposure to excessive pulsatility (266) but also impairs reactivity (260), potentially contributing to repeated episodes of microvascular ischemia and tissue damage. Microvascular ischemia in the brain manifests as white matter hyperintensities, clinically unrecognized focal brain infarcts, and tissue atrophy, each of which contributes to cognitive impairment and frank dementia. Thus, microvascular damage and remodeling may represent a mechanistic link between aortic stiffening, brain lesions and cognitive impairment.

Aortic stiffening is also associated with increased risk for large vessel strokes, which may be ischemic or hemorrhagic (187;224).This may be mediated through atherosclerosis, with increased stiffness contributing both to atherogenesis and risk for plaque rupture (279) or through atrial enlargement and fibrosis, which can trigger atrial fibrillation, providing a cardiac source for embolus (252). 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 blood pressure lability, which is a risk factor for incident stroke (280). Aortic stiffening is associated with atherosclerosis, probably predominantly as a result of atherogenic hemodynamic stresses associated with a stiffened aorta.

Mild cognitive impairment and dementia. Several studies have demonstrated relations between arterial stiffness and cognitive function in selected (194;196;281-283) and community-based samples (191;197;284;285). Increased aortic stiffness is associated with the full range of cognitive impairment, progressing from mild cognitive impairment, which has been demonstrated across multiple cognitive domains, to frank dementia. 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 dementias(192).

Arterial stiffness and the kidneys

Like the brain, the kidneys are low impedance organs that are exposed to 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 that can damage the glomerulus, leading to proteinuria and loss of function (286;287). In addition, a recent study has also demonstrated that such increases in renal pulsatility also correlate with CV and renal outcomes (288). Numerous studies have demonstrated modest but robust associations between increased pulse pressure or pulse wave velocity and reduced glomerular filtration rate (GFR) or proteinuria (200;289-301). However, relations between estimated GFR and stiffness measures are less robust in some studies after adjusting for potential confounders. In a study that measured GFR directly, higher PP was associated with reduced measured GFR. 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, where loss of muscle mass may reduce accuracy of creatinine-based GFR estimating equations (302-304). 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.

Arterial stiffness and hypertension

The association between arterial stiffness and hypertension is well established (305-309). There is a widely held belief that increased aortic stiffness in hypertensive individuals is largely a manifestation of longstanding hypertension-related damage that stiffens the large arteries. A recent analysis from the Framingham Heart Study has shown that higher arterial stiffness, as assessed by cfPWV at an initial exam, is associated with blood pressure progression and incident hypertension 7 years later (305). However, higher blood pressure at an initial exam 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 underscore the importance of better defining the pathogenesis of aortic stiffening (306-309).

A fuller elucidation of basic mechanisms that contribute to increasing pulse wave velocity and pulse pressure may offer insights into targets for development of more effective interventions to prevent or treat hypertension.

Future cardiovascular risk

Stiffening of the central arteries has a number of adverse hemodynamic consequences, including a widening of pulse pressure, a fall in shear stress rate, and increased 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 cardiovascular disease event (190;310). 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 (139;310). 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 blood pressure (209). 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, where an opportunity exists for early identification, lifestyle modification and possible mitigation or prevention of further potentially irreversible deterioration of aortic structure and function (310).

SECTION 4: Arterial Stiffness and Wave Reflections

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Ventricular/Vascular Coupling and Ventricular Afterload

The mechanical "afterload" imposed by the systemic circulation to the pumping left ventricle (LV) is composed of a static (or steady) and a dynamic (pulsatile) component and is an important determinant of normal cardiovascular function and a key pathophysiologic factor in various cardiac and vascular disease states. In the presence of a normal aortic valve, pulsatile LV afterload is largely determined by the elastic properties (arterial stiffness) and wave reflection characteristics of the arterial tree ("arterial load") (1;311-313); the steady component of LV afterload is determined by arteriolar caliber ("arteriolar load").

Although brachial arterial pressure (systolic, diastolic and pulse) is taken as a useful surrogate of arterial function and LV afterload in clinical practice, it should be recognized that: (1) Afterload affects, in a reciprocal fashion, the pressure and flow waves generated by the LV; and (2) Pressure and flow waves are not only dependent on afterload, but are also strongly influenced by LV structure and function (1;311-314). Therefore, LV afterload cannot be fully described in terms of peripheral pressure alone, but should be assessed from central pulsatile pressure-flow relations.

Ventricular-Arterial Interactions

At the beginning of each cardiac cycle, the heart generates a forward-traveling energy pulse that results in increased blood pressure and forward flow in the proximal aorta during early systole (1;205;314). The energy wave generated by the LV (incident or forward wave) is transmitted by conduit vessels and partially reflected at sites of impedance change or mismatch, such as points of branching, change in lumen diameter (taper) and material properties along the arterial tree. Multiple small reflections are transmitted back toward the heart and merge into a "net" reflected wave, composed of the contributions of the scattered backward reflections. This reflected wave is most often portrayed as a single discrete wave, originating from an "effective" reflection site, but is actually the resultant of scattered reflections, originating from distributed reflection sites (1;315). In addition to hemodynamic phenomena related to wave transmission and reflections,

the large elastic conduit arterial system exerts a buffering function, which depends on its compliance and allows it to accommodate additional blood volume during systole without excessive increases in pressure and to release that excess volume throughout diastole without excessive drops in pressure (17).

Quantification of Arterial Load

Analyses of central aortic pulsatile pressure-flow relations (i.e. aortic input impedance spectra) allow the quantification of "steady" or "resistive" load and various components of LV pulsatile load (1;316-318). The steady component of afterload depends largely on mean arterial pressure and the peripheral resistance, which in turn depends on arteriolar caliber, the total number of arterioles that are present "in parallel" and blood viscosity (1;318;319). It can therefore be affected by arteriolar tone, arteriolar remodeling, microvascular rarefaction and endothelial function. Pulsatile LV afterload is, in contrast, predominantly influenced by the properties of larger conduit arteries (both elastic and muscular) and wave reflections. Although pulsatile LV afterload is fairly complex and cannot be expressed as a single numeric measure, key indices of pulsatile LV afterload can be quantified and summarized using relatively simple principles and mechanical models of the systemic circulation, using time-resolved proximal aortic pressure and flow waves (319;320). Time-varying aortic pressure and flow waves can be assessed invasively or non-invasively. The large majority of the early studies on LV pulsatile load were performed in dogs and rats with cuff type flow probes implanted on the ascending aorta and pressure measured with fluid-filled catheter-manometer systems (321) or high-fidelity pressure catheter transducers (322). Later invasive studies in humans were performed using high fidelity pressure-velocity catheters (323-326). Non-invasive assessment of central aortic pressure can now be achieved using high-fidelity applanation arterial tonometry at the carotid artery or by using a generalized transfer function to synthesize an aortic pressure waveform from the radial (or brachial) pressure waveform (1). Aortic blood flow can also be measured non-invasively in humans, using pulsed wave-Doppler ultrasound (327;328) or phase-contrast magnetic resonance imaging (161). The most convenient method to assess aortic inflow is pulsed wave Doppler interrogation of the LV outflow tract, given that systolic LV volume outflow equals proximal aortic volume inflow (328). LV afterload can be assessed in the frequency domain from the aortic input impedance spectrum (calculated from the harmonic components of central aortic pressure and flow waves)

or estimated in the time domain from the central aortic pressure wave (1;311-313;329-331). Input impedance is the “summed” mechanical load imposed by all vessels downstream of a particular point (and which can be fully assessed by measuring time-varying flow and pressure at that particular point) (1;312;316;321;329;332-334). Therefore, “aortic input impedance” represents the summed mechanical load impeding LV ejection. It should be noted that aortic input impedance is not exclusively determined by aortic properties, but depends on the properties of the entire arterial system and wave reflections.

Key parameters of pulsatile LV load include the characteristic impedance (Zc) of the proximal aorta and the amplitude and timing of wave reflections. The Zc of an artery can be intuitively calculated as the sum of higher harmonics of the pulsatile pressure-flow relation or impedance moduli spectrum in the absence of reflected waves. Aortic Zc can also be computed in the time domain as the ratio (P1/ΔQ) (Figure 4.1) (1) where P1 is the amplitude of the first systolic shoulder of the aortic pressure wave and ΔQ is peak aortic flow velocity. Zc is a "local” arterial property (note the difference with input impedance); consequently, Zc measured using proximal aortic pressure and flow represents proximal aortic Zc. An estimate of wave reflection severity (or amplitude) can be obtained from the aortic input impedance spectrum as the first harmonic of the impedance moduli (Z_1) (1;323). It is important to note that the large majority of LV energy (>80%) is contained within the first and second harmonics, therefore, logical therapy to reduce LV energy and reduce myocardial mass should focus on theses lower harmonics.

Wave reflection severity (strength or intensity) is usually accessed via wave separation analysis. This is based on the superposition principle. Reflected waves, by virtue of adding to forward pressure and subtracting from forward flow, distort the linear relationship between the increase in pressure and the increase in flow that is seen in early systole (as a result of the forward wave generated by ventricular contraction) when the pulsatile pressure-flow relation is assumed to be governed purely by ascending aortic Zc (see below).

Effect of Arterial Stiffness and Wave Reflections on LV Afterload

The stiffness of various arterial segments have complex effects on ventricular afterload, through their effects on the early aortic systolic pressure rise, the total compliance of the arterial system and the velocity at which the pulse waves travel forward in the arteries and reflected waves travel backward toward the heart (1;313;335). In early systole, the forward-traveling energy pulse from

LV contraction favors an increase in pressure and forward flow in the proximal aorta. If proximal aortic Zc is high due to a stiff wall, a small aortic diameter, or both, the amount of early pressure (P1) (Figure 4.1) increase is relatively large for any given early systolic flow (1;17;205;312;314). The time of arrival of the reflected wave to the proximal aorta from the lower body depends on the location of reflection sites and on the PWV of conduit arteries which transmits both the forward and backward traveling waves (1;9;312;336). Aortic PWV is directly related to the stiffness of the aortic wall (square root of elastic modulus) and inversely proportional to the square root of aortic diameter (1;9;135;336). Stiffer aortas conduct the forward and backward traveling waves at a greater velocity than compliant aortas and therefore promote an earlier arrival of the reflected wave for any given distance to major reflection sites. The distance to the reflection sites is strongly dependent on total arterial (elastic and muscular) stiffness and body height (or length). In the presence of normal LV systolic function, typical ill effects of increased amplitude and propagation of the reflected wave on the aortic (and LV) pressure waveform include a mid-to-late systolic shoulder which causes an increase in peak (systolic) aortic pressure (and pulse pressure) and the area under the pressure curve during systole (see below) (1;315). Both age and hypertension increase elastic artery stiffness and decrease arterial compliance (1). The total arterial compliance of the systemic arterial tree depends on the summed compliance of the various arterial segments. The compliance of individual vessels is linearly proportional to vessel volume (or radius^3) and, for any given "relative" vessel geometry (wall volume/lumen volume ratio), linearly and inversely proportional to wall stiffness (Young's elastic modulus). The interaction between the stiffness and geometry (including taper) of large elastic and muscular arteries also impacts the characteristics and location of reflection sites. Reflected waves that arrive during LV ejection increase the mid-to-late LV systolic workload, systolic pressure time index, wasted LV energy and myocardial oxygen demand (1;322;331;337). It has also been proposed that the age-related increase in aortic stiffening and wave reflections promotes an excessive penetration of pressure pulsatility into smaller vascular beds in target organs such as the brain and the kidneys (258;317).It should be noted that although the timing of arrival of reflected waves from the lower body to the heart is influenced by aortic stiffness, the relationship between aortic stiffness and reflected wave transit time is relatively poor, presumably given the wide variability in the distance to wave reflection sites. Furthermore, there is not a direct

correlation between aortic stiffness and the amplitude of wave reflections over the entire life span.

Myocardial Wall Stress

Various indices of pulsatile LV afterload are useful because they are meant to be purely reflective of arterial properties (1). However, arterial load should always be interpreted by considering interactions between arteries as a load and the LV as a pump (1;248) and also between myocardial elements and instantaneous LV geometry and the time-varying load imposed by the systemic arterial circulation. Wall stress represents the time-varying mechanical load experienced by the contractile elements in the myocardium (myocardial afterload). Throughout systole, myocardial fiber activation results in the development of tension (stress) and shortening of myocardial segments, which results in progressive ejection of blood from the LV cavity and wall thickening. During early ejection, active development of fiber cross-bridges occurs in the electrically activated myocardium and peak myocardial wall stress occurs (338), because high LV pressure co-exists with quasi-diastolic geometry (relatively thin wall and relatively large cavity). Myocardial fiber shortening and ejection of blood determine a progressive change in LV geometry which causes a drop in myocardial stress (despite rising pressure) during mid-to-late systole. This shift in the pressure-stress relation is probably due to reduced ejection and appears to be necessary for the myocardium to handle the additional load imposed by wave reflections and increased wasted energy, but may be insufficient and/or compromised in the setting of wave reflections of early onset of large amplitude (339;340) and in the presence of lower LV ejection fractions (338). This may be important, because the myocardium appears to be particularly vulnerable to late systolic loading (see below).

As expected from physiologic principles, various arterial properties affect time-varying myocardial wall stress differently. Whereas systemic vascular resistance is a very important determinant of wall stress throughout systole, Zc selectively affects early systole and peak systolic wall stress, wave reflections and total arterial compliance correlate with myocardial stress in mid and late systole and significantly influence the area under the stress-curve generated for any given flow output (340).

Consequences of Pulsatile Afterload on the LV Myocardium

An increase in the pulsatile component of afterload causes an undesirable mismatch between the left ventricle and arterial system, which increases myocardial oxygen demand and decreases cardiac efficiency (238;341). These changes in ventricular/vascular coupling promote the development of LV hypertrophy (LVH) and often lead to both systolic and diastolic myocardial dysfunction (see below) (242;339;342-345). Indeed Jankowski et al (343) reported that the pulsatile but not the steady component of LV load predicted cardiovascular events in coronary patients. Several lines of evidence support the importance of the LV loading sequence (and not just "absolute" load) in LV remodeling and failure (322;337;346). Late systolic loading (and increase in wasted LV energy) has been shown to induce much more pronounced LVH and myocardial fibrosis in an animal model compared to early systolic loading, at identical peak LV pressure levels (322). In humans, reductions in wave reflection amplitude occurring during antihypertensive therapy predict regression of LV mass independently of blood pressure reduction (347). Similarly, animal (249) and human studies (348) have demonstrated an adverse effect of late systolic load on diastolic relaxation. A recent study showed that the intensity of wave reflections, estimated from radial artery pressure waveforms, strongly predicted incident heart failure in the Multiethnic Study of Atherosclerosis (MESA) (349) while another study showed that arterial stiffness and wave reflection predicted cardiovascular mortality (156). The deleterious effects of wave reflections on the myocardium may be due to intrinsic differences in cellular processes between early and late systole. During early ejection, active development of fiber cross-bridges occurs in the electrically activated myocardium and peak myocardial wall stress occurs (338), whereas a transition from contraction to relaxation may occur at the myocardial level in mid-to-late systole, during which increases in load may lead to more hypertrophy (329) and abnormal diastolic relaxation (249;350). The differential effect of time-varying myocardial afterload on cellular processes taking place in early and late ejection should be a focus of further research.

Pressure Differences Within the Arterial Tree and Pulse Pressure Amplification

As the pressure wave travels from the heart to the periphery both systolic and pulse pressures (PP) increase markedly while mean pressure decreases only slightly (~2 mmHg) due to wave reflection and viscous damping (1;351). Thus, both systolic and pulse pressures are greater in the arm and leg than in the ascending aorta (352). This mechanism (PP amplification) ensures that

pulsatile load is lower in central versus peripheral arteries and, therefore, minimizes excessive cardiac pressure energy (or effort) and subsequent pulsatile LV afterload (346). PP amplification (i.e. peripheral PP/central PP) is determined by a combination of factors including LV contractility and ejection duration, heart rate, arterial stiffness (elastic moduli), arterial caliber (and taper), arterial path length timing and amplitude of wave reflections, and arteriolar tone (vascular resistance) (1;351;353-356). These factors are inter-associated making it difficult to determine specific primary modulators. Overall, it would appear that wave reflections explain the largest proportion of the variance in PP amplification with PWV (arterial stiffness), and heart rate making additional notable contributions (351;356;357). Indeed the degree of amplification is age- and elastic artery stiffness-dependent and decreases as aortic stiffness and wave reflection amplitude increase (Figure 4.2A, 4.2B)(357;358). This difference between central and peripheral pressure progression may explain why central aortic pressure is a better predictor of cardiovascular events and outcome than peripheral brachial pressure (156;359-361). Since peripheral muscular arteries stiffen little with age (362-365), elastic properties of these vessels alter amplification minimally. Thus transmission (propagation) characteristics in the upper limbs remain relatively constant (366). However, PP amplification is markedly influenced by changes in smooth muscle tone of muscular arteries. Increased smooth muscle tone (contraction) increases wave reflection and reduces PP amplification while decreased tone (relaxation) has the opposite effect. Reduced PP amplification occurs with aging (1;353;367;368), obesity and disease (hypertension, diabetes, hypercholesterolemia, coronary artery disease) and is associated with traditional cardiovascular risk factors (369;370) and overall vascular burden (371). Moreover, PP amplification is associated with overt target organ damage and regression of target organ damage with therapy (i.e. LVH regression with antihypertensive therapy and exercise conditioning) (372;373), and it independently predicts future cardiovascular mortality (374;375). Thus, PP amplification has been proposed as a potential mechanical biomarker of cardiovascular risk and global arterial function. Racial differences in PP amplification have been reported with African American men having lower amplification than their white peers (376;377) related to increased arterial stiffness and wave reflections (378). Sex differences in PP amplification also exist, with women (particularly post-menopausal women) having lower values than men (379). Reasons for this difference have been ascribed to a host of factors including: shorter stature in women (reduced height resulting in attenuated arterial path length and movement of reflection

sites more proximal), increased PWV affecting timing of the return of the reflected pressure wave, increased aortic taper and arterial impedance mismatch affecting wave reflection magnitude (1;380). Sex differences in PP amplification have been linked to LV diastolic dysfunction in women (242;381). In men and women over age 55 years, the mortality impact of PP amplification is 3-fold higher in women compared to men (379). In younger adults, PP amplification declines as diastolic blood pressure (DBP) rises, offering insight into well noted observations that peripheral PP is unrelated to CV risk in this age cohort (366). Conversely, loss of PP amplification with aging results in peripheral pressures more closely approximating central pressures (Figure 4.2B), increasing the ability of peripheral PP to more accurately predict CV risk in older adults (366). In older adults, PP amplification is predictive of heart failure, ischemic heart disease, atrial fibrillation and mortality (375;382). In young healthy adults, it is also possible for PP amplification to result in spurious systolic hypertension (383). Seen in taller men with compliant vessels, wave reflections are markedly attenuated and PP amplification profound (384;385). The clinical implications of this elevated PP amplification in this population remains to be determined (383). As noted above, heart rate also makes a notable contribution to PP amplification and this is most likely via effects on wave reflection (386;387). With slower heart rate and prolonged systolic ejection duration, there is greater temporal overlap between forward and reflected pressure waves causing an increase in AP and AIx (1). It is estimated that for every 10 bpm reduction in HR, there is an increase in AIx of 4% (387). This in turn results in a reduction in PP amplification. Medications that reduce heart rate such as β-blockers are associated with reduced PP amplification because these drugs cause an increase in wave reflection amplitude (388;389). Interestingly, lifestyle modification that results in bradycardia such as habitual aerobic exercise could possibly result in reduced PP amplification owing to HR-mediated increase in PP from increased wave reflection coupled with reduced arterial stiffness (376;377;390). PP amplification is usually calculated as the ratio of the amplitude of the PP between a proximal and distal site. Alternative methods include calculation of absolute PP differences from peripheral to central sites (peripheral PP – central PP) and expressed as the absolute difference from peripheral to central sites relative to the central site [(peripheral PP – central PP)/central PP]. An issue that remains to be resolved pertains to methodology for central and peripheral PP appraisal. Although the gold standard for PP measurement remains invasive recordings (391;392), this is not practical for routine clinical use.

Current studies noting clinical utility of PP amplification have calculated central PP non-invasively either via: 1) synthesized aortic pressure waves derived from radial pressure waves and a generalized transfer function (GTF); 2) carotid pressure waves as a surrogate for aortic pressure calibrated against brachial mean and diastolic pressure (351). While both methods are valid and have merit, neither is without flaw. Use of the GTF approach requires the radial pressure wave to be calibrated against brachial SBP and DBP. Given additional amplification from the brachial-to-radial sites, this approach has been questioned (393). Compared to radial pressure waves, carotid pressure waves are more technically challenging to obtain calling into question reproducibility and accuracy (351). Moreover, use of an oscillometric cuff to obtain brachial pressures may underestimate diastolic pressures, which would introduce an error into both methods (394). Peripheral PP has been calculated using brachial cuff methods (mostly oscillometric) or radial pressure waves (from applanation tonometry and calibrated against brachial mean and diastolic pressures). Given differences in methodology, norms are currently not available. When using synthesized aortic pressure waves from the GTF approach and brachial pressures obtained from an oscillometric cuff as done in the Anglo-Cardiff Collaborative Trial (ACCT), peripheral PP/central PP varies from 1.7 in the young (< 20 years of age) to 1.2 in the elderly (> 80 years of age) (363). These results are similar to those reported by Bia et al (367) over the same age range in the CUiiDARTE Project and those collected by Nichols et al (unpublished) (see Figures4.2A and 4.2B). When using carotid and radial pressure waves obtained from applanation tonometry as done in the Asklepios Study, PP amplification values tend to be lower (368). Future research is required to standardize measurement as use of aforementioned different techniques can result in a site-specific difference in PP calculation between 14-18 mmHg (395) resulting in slightly different values of PP amplification. Although not without limitation, measurement of PP amplification from noninvasive central and peripheral pulse recordings has proven superior to brachial cuff measures alone when assessing cardiovascular disease (CVD) burden, identifying individuals at risk for CVD events and monitoring response to therapy (371;375). Due to 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 and pulse pressures with various therapeutic approaches is often underestimated by cuff measurements of brachial artery pressure (1;396) (see below).

Components of the Central Aortic Pressure Wave

Figure 4.1 shows invasively measured high-fidelity ascending aortic pressure and flow velocity waves in a normal middle-aged human. The measured aortic pressure (P) and flow (Q) waves are determined by the interaction (or algebraic sum) of a LV ejected forward traveling "incident" wave and a later arriving backward traveling reflected wave from the lower body (Figure 4.3) (1;156;341;397-403). The characteristics of the forward traveling wave depend, primarily, upon the elastic properties (Zc) of the ascending aorta and are not influenced by wave reflections (1;404;405). Two visible demarcations usually occur on the initial upstroke of the central aortic pressure wave in middle-aged and older individuals; the first shoulder (P1) and the inflection point, P_i. 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 while P_i occurs later and denotes the initial upstroke of the reflected pressure wave; this wave represents the second (or mid-to-late) systolic shoulder (see Figure 4.1) (1;331;335;338;340;348;401;405-407). The first shoulder is an estimate of incident (or forward) traveling wave amplitude while the second shoulder is generated by the reflected pressure wave from the lower body with amplitude AP. 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. This relation is used in linear wave separation analysis, which decomposes pressure and flow waveforms into their forward (incident) and backward (reflected) components. Reflection magnitude (RM) is expressed as the ratio of AP and P1 while reflection (or augmentation) index (AIx) is the ratio of AP and central aortic PP. These two variables (RM and AIx) are similar and are measures of wave reflection strength (or intensity) (1;404;405). When the first shoulder and P_i occur simultaneously, as often occurs in older individuals and patients with severe hypertension, no demarcation is visible (see Figure 4.4). Therefore, if pressure and flow velocity are measured simultaneously, P1 and P_i can be determined and AP calculated. If flow velocity is not measured and P_i is not visible, a method that uses the second (or fourth) derivative of the pulse to identify P_i is used. In this method, P_i occurs at the second peak of the second derivative (1;401). In younger individuals the second systolic shoulder occurs much later than the first and is of lower amplitude (1;324). In a system with no reflections (e.g. very

compliant or very long) the flow and pressure waves are similar in shape (see Figure 4.3). The characteristics of the reflected wave depends upon a more complex set of determinants than the forward wave, namely, the physical properties (stiffness, taper and branching) of the entire arterial tree (elastic plus muscular arteries and arterioles), PWV, the round-trip travel time (Tr) of the wave from the heart to the periphery and back, and the distance to the major "effective" reflecting site in the lower body (1;316;324;330;406;408). AIx is related to arterial properties via changes in PWV from the heart to the termination of vessels in the lower body. Increased arterial stiffness increases PWV and causes early return (Tr decreases) of the reflected wave from lower body reflecting sites to the heart during systole when the ventricle is still ejecting blood (1;315;335;338;409;410). Arterial stiffness, through its effect to decrease Tr results in an increase in AP and systolic duration. This mechanism augments ascending aortic systolic and PP (91;343;411-414), an effect that increases arterial wall stress, potentiates the development of coronary artery atherosclerosis, elevates LV afterload, and increases LV mass and oxygen demand while decreasing stroke volume (341;372;373;406). Since the reflected wave and associated boost in pressure (LV and aortic) does not contribute positively to ejection of blood, the effect of the extra workload is wasted (pressure) energy (or effort) (339;347;404;406;415-417) the ventricle must generate to overcome the augmented aortic pressure. Accordingly, optimal treatment for high central systolic and PP (pulsatile component of LV load) should focus not only on increasing arteriolar caliber and reducing peripheral resistance (steady component of LV load) but also on reducing arterial stiffness, PWV, systolic wave reflection and Ew (418;419). Correct calculation of these variables (that is, AIx, forward and reflected wave amplitude and travel time, distance to reflection sites, and Ew) depends on the accurate determination of P_i (see above) (1;328;401). Also, care must be taken when using AIx as a measure of arterial stiffness because of its dependence on heart rate, ejection duration and body height (1). In general, RM is used in the frequency domain while AIx is used in the time domain as a measure of wave reflection intensity (1). Since invasive recordings of ascending aortic pressure waves and pulse wave analysis can only be made in a selected number of patients in the catheterization laboratory, techniques have been developed recently that enable the non-invasive determination of the above variables (156;347;356;405) in large cohorts with similar results (341;389;411;412;420-422). Some studies use the carotid artery wave as a surrogate for the central aortic pressure wave while others derive it from the radial artery wave using a GTF.

Briefly, radial artery pressure waves are recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms are acquired and ensemble averaged, a validated GTF is used to synthesize the central aortic pressure wave non-invasively. To obtain the GTF, 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 using data obtained from previous invasively measured aortic pressure waves (1;356;405). Large observational trials such as the Baltimore Longitudinal Study of Aging (43), Framingham (336;423) and Anglo-Cardiff (ACCT) (363) and many other aging studies (358;365;424-426) and reviews (400;419;427) observed that age is an important determinant of arterial properties and wave reflection characteristics that influence dramatic changes in both central and peripheral blood pressure. In youth, the reflected wave from the lower body travels at a reduced PWV and arrives at the heart in diastole (Figure 4.4, top) which aids coronary artery and myocardial perfusion, but with increasing age (Figure 4.4, middle and bottom), the elastic arteries stiffen, increase PWV and cause the reflected wave to arrive at the heart during systole (second shoulder) with greater amplitude and systolic duration. This modification in wave reflection characteristics causes a decrease in stroke output (negative reflected wave during deceleration) and a corresponding decline in cardiac output (428). Aortic systolic and PP pressure increase with age whereas diastolic pressure increases to middle age and then decreases in later life (43;363;423;428).In the three individuals shown in Figure 4.4, PP in the radial (and brachial) artery doubled, whereas PP in the ascending aorta, because of wave reflection, tripled, causing amplification to decrease from 1.7 to 1.1 (see (363;429) and Figure 4.2B). Because of increased central elastic artery stiffness, the reflected wave from the lower body migrates (leftward in Figure 4.4) into systole and increases aortic AP and AIx; in the radial and brachial artery, since stiffness changes very little with age (362;364;365;430), the forward to reflected wave (from the hand region) ratio remains essentially unchanged. Wave reflection characteristics are amplified in older individuals and in patients with systemic hypertension (364;431) thereby, causing a reduction in PP amplification. This explanation of wave reflection characteristics and the associated effects on central aortic pressure wave morphology in systole and diastole is accepted by most but not all (432). In a system with no reflections or one in which the reflected wave arrives after peak systolic pressure and with low amplitude, an increase in aortic stiffness alone only causes an increase in aortic PP (for a given stroke volume), with little change in wave

contour (see Figure 4.3). Major changes in aortic pressure wave contour are due to alterations in amplitude and timing of wave reflections from the lower body including both elastic and muscular arteries. LV afterload, central aortic and brachial artery systolic and PP, and AIx are increased by elastic artery stiffening and increased wave reflection amplitude, all of which are alterations associated with aging and hypertension (363;423) and resulting in LVH (322;367;373;433-437) and arterial wall damage—major cardiovascular, cerebrovascular, and renovascular risk factors (156;157;197;258;281;317;411;413;414;431;438-443). Cardiovascular risk factors include coronary artery atherosclerosis, decreased coronary blood flow and coronary flow reserve (CFR), LVH, heart failure and mortality. An explanation for the progression from normal LV systolic function to severe failure is available on the basis of the argument proposed by Westerhof and O'Rourke (1;444). This explanation has been effectively used to characterize mechanical pumps, with the LV seen to act as a flow source (powerful ejection) in youth when the ventricle is optimally matched to a compliant arterial system and power generation is minimal and wasted energy is zero. Under these circumstances the reflected wave arrives in diastole (Figure 4.4 and Figure 4.5A) and aids in coronary artery perfusion and coronary flow reserve (CFR). The age-related increase in elastic artery stiffness (and PWV) causes the reflected wave to arrive earlier to the heart and boost pressure in mid-to-late systole and places an extra pulsatile workload on the LV causing it to generate more force, which is wasted energy (339). These changes in arterial properties and wave reflection characteristics cause the LV to change from a flow source to a combined flow and pressure source (ejection limited by pressure achieved) as hypertension develops (Figure 4.5B). As the elastic arteries become stiffer LV pressure increases and causes an increase in systolic pressure time index (SPTI) and myocardial oxygen demand. Sustained elevation and prolongation of mid-to-late systolic augmentation results in LVH (346;445;446), which is associated with progressive degenerative changes in the myocytes such that these weaken and develop less force with each contraction. The weakened, hypertrophied fibers lengthen and the LV dilates, with augmented systolic pressure and stroke output initially being somewhat maintained (Figure 4.5C) at greater muscle length and LV volume through the Frank-Starling mechanism (1;330). The LV ejection fraction in these patients is usually ≤40%. Ultimately, compensation is lost and the LV cannot generate the extra force necessary to completely overcome the mid-to-late systolic augmented pressure. AP, AIx, and systolic (and pulse) pressure are therefore reduced and associated with a decrease in ejection

duration, Ew, SPTI, and stroke volume (447). The LV ejection fraction in these patients is usually <35% (448). When LV contractility is severely impaired, wave reflection does not boost systolic pressure (Figure 4.5D) because the heart is incapable of responding, so that systole is terminated prematurely, and wave reflection is seen to have had a negative influence on flow rather than a positive influence on pressure (330;448); and the LV reverts back to a flow source (weak and abbreviated ejection) as heart failure progresses and PP decreases (339;447). Indeed, data from a large nationwide cardiology database (IN-CHF Registry) indicate that a low PP is an independent predictor of mortality in heart failure (449). In severe heart failure there is a direct positive relation between ejected flow and generated pressure, therefore, an improvement in hemodynamics will be viewed as an increase in ejection duration, AP, AIx, PP and SPTI (Figure 4.6) (1).

An increase in arterial pressure pulsatility resulting from arterial stiffness and wave reflection has little effect on the systemic circulation to most bodily tissues because their flow is determined by mean pressure, and because cells are protected by the vasoconstricted small arteries and arterioles upstream (317). The brain and kidney cells receive no such protection because arterial vessels remain dilated. The large increase in arterial pressure pulsatility is applied to all the distributing arteries in these organs while mean flow is maintained (450). Brain and kidney arteries of all sizes are thus subjected to higher pulsatile circumferential stress and higher longitudinal shear stress. Their ability to withstand increased stresses depends on their resilience, and this is markedly decreased in a number of diseases, particularly diabetes mellitus (1;451). Aging changes of large arteries thus promote a “set-up” for small arterial disease and the types of changes elucidated by Byrom (450;452) over 50 years ago. Byrom’s work was initially conducted in rats but was applied to the small-vessel disease seen in human hypertension. He showed that damage to small arteries could be induced by increased pulsatile stress and could lead to tearing of their endothelial and smooth muscle cells with disruption of the vessel. He thus explained development of small arterial dilations and aneurysms, and the features of lipohyalinosis and of fibrinoid necrosis as seen in the brains and kidneys of hypertensive disease. Byrom further showed that these changes were largely reversible when disrupting forces were reduced (452).

Peripheral Artery Pressure Waves

Peripheral wave reflections are greater than central wave reflections and increase somewhat from brachial to radial vascular beds owing to altered timing of wave reflections and altered location of reflection sites (1;404). This observation has also been confirmed with wave intensity analysis (453). In the arm, PP pressure amplification and contour are strongly influenced by wave reflection from both reflection sites in the hand and in older individuals, distal reflection sites in the lower body (1). The brachial and radial artery pressure waves are composed of three waves: a forward traveling wave generated by blood flow and two reflected waves, one from the hand region (owing possibly to larger basal vasoconstrictor tone where circulation occurs through the skin) (453) and a later arriving wave from the lower body region (404). As the elastic arteries become stiffer (e.g. with age and hypertension), aortic PWV increases and the reflected wave from the lower body returns earlier to the brachial and radial arteries, migrates up the pressure wave toward peak systolic pressure and in very elderly individuals (usual >80 yrs) adds to the other two waves and increases systolic and PP (see Figure 4.4). Since the aging process modifies the distensibility of elastic but not muscular arteries (362;363) the observed morphological changes in peripheral artery pressure wave contour are due primarily to reflected waves from the lower body. Peripheral augmentation index obtained from the radial pulse is highly correlated with central AIx measured invasively and non-invasively (r=0.86 – 0.96) (404;454-457) and changes in peripheral augmentation index closely approximate changes in central AIx during pharmacologic perturbation (457;458). Radial augmentation index is calculated as the ratio of the late systolic peak of the radial pressure wave to the early systolic peak pressure (P2/P1) (see Figure 4.4). Similar to results obtained from central pressure waveforms, radial augmentation index increases with age, is higher in women and is associated with height and heart rate (459). Radial augmentation index has been demonstrated to be clinically useful in the prediction of LVH (337) and reveals premature coronary artery disease (CAD) in younger men (460). Moreover, peripheral augmentation index defines the relationship between central and peripheral PP (457). That is, central augmentation is tightly coupled with peripheral amplification as peripheral augmentation index is the amount by which the central pressure is reduced relative to peripheral pressure. A reason for this may be related to timing of wave reflections as radial P2 occurs at a time devoid of significant wave intensity (after genesis of the forward/compression pressure wave and prior to genesis of a forward expansion wave owing to myocardial shortening and subsequent aortic valve closure) (461). Because of this, it

has been postulated that the second systolic peak (late systolic shoulder) of the radial pressure waveform correlates well with the second systolic shoulder of the aortic pressure wave (both are produced by the same reflected wave from the lower body) (404;462). Indeed radial P2 has been shown to closely approximate central systolic BP in some (457;458;463) but not all studies with lower accuracies being reported at lower arterial pressures (463) and in persons with central aortic pressure waves where the second systolic shoulder is lower than the first (Type C wave) (1;464). Despite this, radial P2 compliments GTF-derived central aortic pressures and is associated with target organ damage (LVH and carotid IMT) independent of brachial blood pressure (465).

Effects of Increased Aortic Stiffness and Wave Reflection on the Coronary Circulation

CFR is defined as the ratio of blood flow at maximal (or near maximal) vasodilation and basal (or resting) blood flow (466). Vasodilation results from relaxation of smooth muscle cells of the microvascular circulation and is associated with endothelial function. Therefore, in the absence of obstructive epicardial coronary artery disease, a reduction in CFR is frequently used as an index of microvascular (or endothelial) dysfunction (467-469). CFR is strongly dependent upon changes in the plateau level of basal myocardial perfusion. For example, in LVH total basal coronary flow is increased but maximal flow does not change, therefore, CFR is reduced (466;469-471). To fully appreciate the importance of coronary microvascular physiology, it must be realized that coronary blood flow changes dramatically during the cardiac cycle. Since the rhythmic contraction of the LV compresses and squeezes the coronary vessels and throttles blood flow during systole the majority of flow (about 80 %) occurs during relaxation (or diastole) (472). As central aortic stiffness and wave reflection amplitude increase, central systolic blood pressure rises, PP widens, and LV wall stress and myocardial oxygen demand increase while aortic diastolic pressure decreases (363;423;473;474). These alterations in pulsatile load cause LVH independent of change in the steady load component (322;475). Such abnormalities in ventricular/vascular coupling unbalance the favorable myocardial oxygen supply/demand ratio and promote myocardial ischemia and contractile dysfunction (1). In the normal coronary circulation blood flow is maintained over a wide range of perfusion pressures by the process of autoregulation - as perfusion pressure falls vasodilation occurs and maintains a near normal coronary blood flow (466;469). Information regarding the ill effects of aortic stiffening and wave

reflections on the coronary circulation has come primarily from experimental animal models where the dog aorta was artificially stiffened or replaced with a rigid tube (240;476-478). In these studies when the heart ejected into a stiff or noncompliant aorta, systolic and PP, wasted LV energy and myocardial oxygen demand increased and diastolic pressure decreased but coronary blood flow also increased in response to the increased oxygen demand and myocardial contractile function was maintained at rest. However, increased aortic stiffness and wave reflection caused a decrease in CFR and during increased myocardial contractility endocardial blood flow was impaired and the subendocardial electrocardiogram showed signs of ischemia (477). These undesirable alterations in ventricular/vascular coupling were enhanced in the presence of a high-grade coronary artery stenosis (476) and during reductions in aortic diastolic blood pressure (479). During total coronary artery occlusion and myocardial ischemia increased aortic stiffness caused marked enhancement in cardiac dysfunction (240). In the acute post-myocardial infarction period, lowering aortic diastolic blood pressure below 80 mm Hg with intravenous nitroglycerine resulted in an increase in myocardial infarct size (480). In more recent experimental rat studies, Hachamovitch et al (481), Gosse et al (470) and Susic et al (482;483) found that age and hypertension, conditions associated with increased aortic stiffness and wave reflection strength, produced LVH and adversely affected the coronary circulation and CFR. These changes in coronary hemodynamics in response to increased aortic stiffness increase the potential for ischemic episodes, especially in the subendocardial region (481).

Several studies in humans have confirmed and expanded the findings in experimental animal models. The age-related increase in aortic stiffness and wave reflection, in healthy volunteers with presumably normal coronary arteries, causes an increase in LV afterload and resting coronary blood flow, but a decrease in CFR (484). Similar results have been reported in patients with essential hypertension and increased LV mass (485). The majority of older patients have increased aortic stiffness and wave reflection which cause increased systolic blood pressure and decreased diastolic pressure resulting in isolated systolic hypertension so that aggressive treatment to lower blood pressure is more difficult (423;486;487). In patients with LVH and significant CAD associated with increased aortic stiffness and wave reflection, acute lowering of diastolic blood pressure to less than 85 mm Hg. may increase myocardial ischemic events (488;489). These investigators warned against excessive lowering of diastolic blood pressure in high risk CAD patients. Is there a point beyond which diastolic blood pressure reduction is

dangerous (i.e. is there a J-or U-curve phenomenon for diastolic pressure)? Numerous studies and clinical trials have shown a definite J- or U- shape relation between cardiovascular events (and outcome) and aortic diastolic pressure during anti-hypertensive treatment (474;490-492). It has been postulated that the most probable explanation for this relation is that subjects who have severe CAD have a poor CFR (489), which makes the myocardium primarily and linearly dependent upon coronary perfusion pressure for myocardial blood supply because autoregulation is completely exhausted; however, the jeopardized region may receive some blood flow through collaterals (406). In other studies, significant correlations between CFR and increased aortic stiffness and wave reflection strength were demonstrated in different patient populations, some with (493) and others without (494-497) CAD. The decrease in coronary blood flow and CFR in CAD results predominantly from narrowing of epicardial coronary arteries while reduction in CFR in patients with normal or non-obstructive CAD is more difficult to explain. Therefore, one must consider other factors than coronary artery narrowing such as myocardial oxygen demand (498), diastole pressure time index (DPTI) (499), coronary pressure gradient and coronary artery endothelial function (microvascular dysfunction) (500). Arterial stiffness and wave reflection affect all four of these variables and can readily explain angina pectoris even in the absence of macrovascular epicardial coronary artery atherosclerosis (501-504). Increased stiffness of central elastic arteries with aging (and hypertension) and/or vasoconstriction of peripheral muscular arteries increases central aortic pressure (systolic and pulse) to a much greater extent than brachial cuff pressure because of wave reflection (1;330) (see Figure 4.3); central and brachial diastolic pressures decrease in parallel. These hemodynamic changes cause an increase in myocardial oxygen demand during systole while decreasing coronary artery perfusion in diastole. Such chronic changes in LV afterload are associated with a reduced impedance mismatch and an undesirable imbalance in the myocardial oxygen supply/demand ratio which is exacerbated in LVH and can lead to ischemia and angina even in the absence of coronary atherosclerosis (504). Similarly, a marked increase in heart rate in the face of increased aortic stiffness can reduce coronary perfusion and precipitate myocardial stunning (505). Aortic stiffness and wave reflection can have a profound influence on coronary blood flow and CFR through an elevation in systolic pressure, a slowing in LV relaxation and a reduction in diastolic pressure (348;506). These effects can be estimated as the “subendocardial viability ratio” (DPTI/SPTI) which has been shown to be directly related to CFR (472;507). Clinical information

on the effects of arterial stiffness and wave reflection on epicardial coronary artery blood flow waveforms and CFR has come from both invasive (Doppler catheter or guidewire) and non-invasive (transesophageal and transthoracic Doppler echocardiography) measurements (467;496;507-509). Regardless of the method used to measure coronary blood flow velocity and aortic distensibility, the results are similar: aortic stiffness and wave reflection amplitude are both inversely related to CFR in the presence or absence of CAD. Results from the Dallas Heart Study (504) showed that angina among women in the general population is common and is not necessarily associated with subclinical atherosclerosis. However, angina in the absence of subclinical atherosclerosis is not related to traditional atherosclerotic risk factors but is associated with clinical, inflammatory, and vascular factors that reflect endothelial dysfunction and increased aortic stiffness and wave reflection, suggesting a distinct vascular etiology and alternative potential therapeutic targets. Furthermore, coronary microvascular dysfunction in some cases, however, may be independent of the endothelium (510). Thus, Reis et al. (511) of the Women Ischemic Syndrome Evaluation (WISE) study group reported that of 159 women without significant obstructive CAD undergoing invasive studies (velocity guidewire) , 74 (47%) had what they defined as subnormal coronary flow responses to intracoronary adenosine (CFR<2.5). Age and the number of years postmenopausal correlated inversely with reduced CFR, but not lipid and hormone levels, blood pressure, or left ventricular ejection fraction. A subsequent report from the WISE study group with 210 women undergoing this testing indicated that conventional atherosclerosis risk factors accounted for <20% of the observed variability in CFR, suggesting the role of other yet-unidentified factors responsible for microvascular dysfunction (512).

Modification of Wave Reflections with Pharmacological and Non-pharmacological Interventions

Pharmacological Interventions

In the evaluation of intervention (pharmacological and non-pharmacological) on cardiovascular function any conceptual model (including Windkessel) that excludes wave reflection characteristics cannot be regarded as realistic and thus will show serious deficiencies with change in cardiac and arterial function (1). Pharmacological interventions (or treatments) which

are able to reduce arterial stiffness and wave reflections, the primary cause of elevated systolic blood pressure and LVH, include drugs prescribed for the treatment of hypertension, hyperlipidemia and heart failure.

Different cardiovascular drugs have different effects on arterial properties (structure and function) and wave reflection characteristics (388;389;513;514). Anti-hypertensive drugs are usually classified as vasodilators, aldosterone blockers, β-blockers and diuretics (91;435;439;487;515-523). In most countries, thiazide diuretics are the cheapest antihypertensive drugs available and they are the recommended first-line treatment for hypertension in the US (524). Diuretics and pure β-blockers decrease blood pressure by decreasing blood volume and cardiac output, respectively, but have little, if any, direct (active) effect on arterial properties and wave reflection characteristics. Pure β-blockers increase wave reflections while diuretics have no effect (388;525). Third generation β-blockers have vasodilator effects mediated by α1-adrenoceptor antagonism. These agents have been shown to decrease aortic stiffness and reduce AIx (526-528). Selective and nonselective aldosterone blockers attenuate cfPWV and AIx (529;530) in select patient groups by increasing nitric oxide (NO) bioactivity and improving endothelial vasodilator dysfunction (531)

Vasodilator drugs include Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARB), Calcium Channel Blockers (CCB), aldosterone antagonists and nitrates. Arteriolar vasodilators, such as hydralazine and dipyridamole, primarily increase arteriolar caliber and therefore decrease peripheral resistance and mean arterial pressure via their action on arteriolar smooth-muscle cells with little effect on aortic wave reflections (532). Arterial vasodilators, such as nitrates, primarily relax smooth muscle cells in large conduit muscular arteries and therefore decrease arterial stiffness, aortic wave reflection amplitude and duration and reduce central systolic and PP with little change in brachial cuff systolic and PP (Figure 4.7) (533-537).These drugs are seldom used to treat systemic hypertension except in emergencies, however, the combination of hydralazine and nitrates is frequently used in the management of heart failure in African-American patients (538). Dual (arteriolar and arterial) acting vasodilator drugs such as ACE inhibitors, ARBs and CCBs are the most commonly used vasodilators for lowering blood pressure. Although vasodilators reduce wave reflection amplitude and central aortic systolic pressure they probably have little direct effect on stiffness of elastic arteries as large as the human aorta independent of blood pressure reduction (1;388)

Some studies question this claim (34;539;540). The main finding of the recently reported meta-analysis that treatment with ACE inhibitors in patients with arterial stiffness caused by different pathological conditions improved the stiffening of the arteries as reflected by PWV and reduced arterial wave reflections as assessed by AIx when compared with placebo (523).Acute reduction in AIx can be achieved by drugs that actively dilate conduit muscular arteries accompanied by the passive effects on the aorta (i.e. lowering mean blood pressure) (406).These separate actions decrease pressure wave (forward and reflected) propagation along the entire arterial tree and improve wave reflection characteristics. Vasodilator drugs reduce wave reflection via delayed return of the reflected wave from the lower body to the heart while decreasing its amplitude and systolic duration (541-544). Morphologically, the reflected wave (second systolic shoulder) which is superimposed upon the aortic pressure wave decreases in amplitude and the wave migrates somewhat rightward with vasodilation. These modifications of reflected wave characteristics reduce central systolic and PP, AP, AIx, wasted LV pressure energy, and SPTI which leads to regression of LVH and improvement in ventricular/vascular function and myocardial oxygen demand (545;546).The beneficial effects of these drugs on wave reflection characteristics can occur with or without a decrease in aortic stiffness (1;547). Because of wave reflections, the effects of vasodilator drugs on brachial and radial artery systolic and PP are much less pronounced than their effects on central hemodynamics (1;516). This is illustrated in Figure 4.8, which shows a hypertensive patient’s response to the ACE inhibitor lisinopril. Lisinopril caused a 25 mmHg decrease in brachial cuff systolic blood pressure and a 36 mmHg decrease in central systolic aortic pressure; PP amplification increased from 1.2 to 1.5. Differences in central and peripheral pressure-lowering effects by vasodilator drugs, as illustrated in Figures 4.7 and 4.8, strongly suggest that the beneficial cardiovascular effects of vasodilator drugs has been grossly underestimated in previous studies that measure brachial artery cuff BP with no central aortic pressure determination (519;548-550). This contention was verified in the REASON (ACE inhibitor/diuretic combination vs β-blocker) at one year (541;544), CAFÉ (substudy of ASCOT, ACE inhibitor/CCB combination vs β-blocker/diuretic combination, duration) at six years (551), EXPLOR (CCB/ARB combination vs CCB/β-blocker combination) at six months(552) and AORTA (azelnidipine/ARB combination vs amlodipine/ARB combination) at 24 weeks(546) clinical trials. ACE inhibitors, CCBs and ARBs (and their combinations) all decreased synthesized central aortic systolic and PP significantly by reducing wave reflection amplitude

and increasing PP amplification. Also, a more recent randomized trial in patients with chronic kidney disease (CKD) reported that the combination of an ACE inhibitor and an ARB significantly reduced aortic stiffness and AIx and increased PP amplification (91). Based upon the above observations, the apparent "pressure-independent" benefits of vasodilator drugs in clinical trials such as the HOPE trial (ACE inhibitor vs placebo) (548) may occur in response to unmeasured but significant reductions in central (but not peripheral) systolic and PP. Accordingly, it would be expected that the beneficial effects of ACE inhibitors, including regression of LVH (435;545), are not really independent of changes in arterial blood pressure, simply that the cuff sphygmomanometer method does not measure the central aortic blood pressure (i.e., the pressure the heart pumps against). The same reasoning can easily explain why the ARB losartan was more effective than the β-blocker atenolol in reducing LV mass and cardiovascular mortality in the LIFE trial (ARB vs β-blocker; duration four years), (553;554) even though, after a decade, the authors still will not accept the fact (518;519). In the LIFE trial, atenolol and losartan reduced brachial systolic, mean and PP and total peripheral resistance by the same amount, however, central aortic blood pressure was not determined. In a similarly designed study Dhakam et al (555) found that the ARB eprosartan and atenolol reduced brachial cuff blood pressure the same amount but reduced central aortic pressure significantly more. Also, in this study wave reflection amplitude was reduced by the ARB but was increased by the β-blocker.

Non-pharmacological Interventions

Proposed non-pharmacological interventions which may reduce arterial stiffness (cfPWV) and wave reflections (AIx) include aerobic exercise training (556-560) (561;562), dietary changes (including weight loss and salt reduction) (438;563-567), passive vibration (568) and enhanced external counterpulsation (EECP) treatment (417;569;570). For maximum cardiovascular benefits these interventions must be initially introduced acutely but continued over an extended period of time.

During high physical activity or acute bouts of aerobic exercise heart rate, LV contractility and stroke volume increase while peripheral arteries and arterioles dilate and thus cause a decrease in peripheral arterial stiffness and vascular resistance (376;457;571;572). These changes in cardiovascular function cause an increase in peak ascending aortic blood flow and arterial blood

volume resulting in an elevation of systole, diastolic, mean and pulse pressures and an improvement in wave reflection characteristics. Wave reflection improvement is manifested in the aortic input impedance spectrum as a reduction in the lowest frequency harmonic, Z_1 (326;332;333;573) and in wave reflection amplitude (and AIx) (457). In young subjects (dogs and humans) aortic stiffness (PWV and Z_c) does not change, however, in middle-aged subjects there is a paradoxical increase in aortic stiffness and a decrease in wave reflection amplitude and vascular resistance; in old age there is also an increase in wave reflection amplitude and wasted LV energy (416;574). These alterations in wave reflection characteristics in young and middle aged subjects have a favorable effect on ventricular/vascular coupling via a reduction in afterload and LV wasted energy and may ultimately have a favorable effect on exercise capacity and physical function. The inability to reduce pressure from wave reflections during exercise is associated with reduced LV function in patients with heart failure (575). The CCB verapamil has been shown to reduce pressure from wave reflections and this is associated with improved exercise tolerance in older adults (576). Reduced wave reflections during and immediately after exercise, coupled with increases in peak aortic blood flow (and hence forward wave pressure genesis), and increases in heart rate, result in substantial amplification of the pressure pulse wave from the heart to the periphery. Aging increases aortic stiffness and results in attenuation of PP amplification during exercise owing to lessened reductions in pressure from wave reflections (574;577). Nitric oxide mediated dilation does not appear to be the primary responsible mechanism for reductions in wave reflection amplitude and increases in PP amplification during acute bouts of light aerobic exercise as NO blockade with N(G)-monomethyl-l-arginine does not alter the central hemodynamic response to exercise (578). During cool-down from submaximal exercise heart rate, stroke volume and cardiac output decrease and approach pre-exercise levels. Moreover, there are reductions in central artery stiffness and pressure from wave reflections because of peripheral vasodilation (579;580). However, following higher intensity dynamic exercise such as short sprint cycling, there may be increases in arterial stiffness (581;582). In sedentary people with coronary artery disease, coronary thrombosis (and obstruction) is more likely to occur during a burst of activity or shortly after it than during a comparable period of rest. In people who take regular exercise, coronary occlusion and myocardial infarction are less frequent and do not show the increased incidence with exercise (583;584).

Multiple studies attest to the benefits of habitual physical activity and regular aerobic physical exercise training for vascular health in advanced age, hypertension, diabetes, coronary artery disease and heart failure (1;561;571;583;585-594) and to the improvement in oxygen extraction from blood, and in cardiovascular function that occur with exercise training. It should be noted that not all studies note favorable reductions in arterial stiffness with aerobic exercise training. Arterial stiffness may not be modifiable with aerobic exercise training in older obese adults (595) or older adults with isolated systolic hypertension (596;597), owing to higher baseline arterial stiffness in these populations. Although isolated reports of increased arterial stiffness in select chronically endurance exercise trained populations exist (i.e. marathon runners) (598), the majority of cross-sectional studies to date note that habitually physically active individuals, individuals with high aerobic fitness and endurance athletes have lower arterial stiffness (higher arterial compliance) then their sedentary counterparts (585;587;599-601). With regard to pressure from wave reflections, when performing aerobic (endurance) exercise such as jogging or running, fast or brisk walking, swimming or cycling it is important to maintain a continuous target heart rate over multiple sessions. Target heart rate is considered 60-80% of one's maximum heart rate (220–age). Cross-sectional studies of aerobic exercise trained individuals are conflicting and have reported both reduced pressure from wave reflections (562;574;585), no difference (602;603) and increased pressure from wave reflections (377;390). These differences in wave reflection characteristics may be linked to lower heart rates in the endurance trained subjects. For example in the study by Laurent et al (390), athletes had a higher central systolic and PP than sedentary controls but they also had significantly reduced heart rate (– 17 beats/min) and aortic PWV (– 2.0 M/sec). The increase in pressure is probably due to an increased P1 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 (561;604) or no change (589). Although endurance exercise training has been shown to reduce arterial stiffness and improve peripheral vascular tone and endothelial function, exercise training-mediated reductions in heart rate (376;377) and improvements in LV contractility (432;590;605-607) likely equipoise potential to detect a reduction in pressure from wave reflections consistently across studies. There is no doubt that weight loss and regular exercise lowers LV afterload (static and dynamic components) and heart rate, enhances quality of life and reduces morbidity and mortality from cardiovascular events (571;608-611). 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. They are less likely to experience the same surge in blood pressure or in heart rate if a burst of exercise is necessary in normal daily activities (1). In older individuals, one year of exercise training was found to significantly improve physical fitness and lifetime risk for cardiovascular disease without affecting endothelial function or arterial stiffness (612). Improved endothelial function with exercise is now established (376;377;588;590;605;606;611). The cause of the improvement is probably due to the periodic increased shear stress on the vascular endothelium that accompanies exercise (613). It is possible that the same mechanism (measured periodic shear stress on endothelium) is responsible for the favorable effects of enhanced external counterpulsation (EECP) (417;569;570). Improvement in endothelial function in both exercise and EECP (417;561;609) is associated with reduction in peripheral PWV and aortic wave reflection amplitude. Improvement in endothelial function may explain the benefits of 'passive exercise' and of sessions of external counterpulsation in refractory angina (568;614).

Acute resistance exercise imposes a very different stress on the CV system than aerobic exercise. While aerobic exercise induces a volume load, on the heart and other organs, resistance exercise imposes a pressure load. Acute resistance exercise increases pressure from wave reflections and unlike aerobic exercise, resistance exercise increases aortic stiffness and reduces pulse pressure amplification (605;615-617). During resistance exercise skeletal muscle compression of the underlying vasculature will create physical reflection sites, altering timing and amplitude of pressure wave reflections. This manifests as an increase in the AIx (615). During high intensity resistance exercise, performance of a Valsalva maneuver becomes unavoidable (618). Immediately post-release, strong wave reflections are detected in the aorta (1). Thus, increases in vascular resistance from muscular compression coupled with performance of a Valsalva maneuver contributes to increased afterload with this exercise modality via augmentation of pressure from wave reflections. A change in timing of pressure from wave reflections during resistance exercise is a strong predictor of LV mass in hypertension (338). The effect of resistance exercise training on central artery stiffness remains controversial. Cross sectional studies have reported lower carotid artery compliance in strength-trained athletes (619). However aortic PWV may not be different between strength trained athletes and their sedentary peers (620;621) or may even be lower in strength trained athletes (622). A recent meta-analysis

concluded that high intensity resistance exercise training is associated with increases in central artery stiffness in those with lower baseline stiffness values (623) although this remains contested (376;624-626). Resistance exercise training has been shown to increase pressure from wave reflections (627) but the majority of studies note no effect (376;625;626;628-630). Studies that combine both aerobic and resistance exercise training note no change in central artery stiffness (assessed with carotid-femoral PWV or carotid ultrasonography) (631;632) or pressure from wave reflections assessed using the augmentation index (633).

While the effects of exercise on arterial stiffness and wave reflections have been studied for more than half a century (634), many aspects still remain unclarified. It appears that the effects depend on the type of exercise (aerobic or resistance), on the intensity, on the duration of the exercise stimulus (acute versus short-term versus long-term), on the baseline arterial properties (stiffer vessels versus more compliant vessels), on the vascular bed assessed (central elastic arteries versus peripheral muscular arteries) and on the population studied (younger versus older, lean versus obese, normotensive versus hypertensive etc.). Future studies that make use of additional technologies and techniques to assess vascular structure, function and wave reflections (e.g. MRI, wave separation analysis, wave intensity analysis) may provide some clarity into this opaque and ever-evolving literature.

ARTERIAL STIFFNESS AND WAVE REFLECTIONS

Legends

Figure 4.1 High fidelity pressure (P) and flow (Q) waveforms measured invasively with a multi-sensory cardiac catheter in the ascending aorta of a middle-aged subject. P_i is an inflection point that indicates the beginning upstroke of the reflected pressure wave (second or late systolic shoulder) with amplitude AP and duration (ED–Tr). This enclosed area (Ew) represents energy wasted by the ventricle during ejection. Tr is the round trip travel time of the forward (or incident) wave (amplitude P1, first or early systolic shoulder) from the ascending aorta to the major "effective" reflecting site in the lower body and back. The forward and reflected waves add together (superposition) to give the measured pressure wave with pulse pressure (PP) = (P1+AP). ED is ejection duration. Note that pressure after the inflection point continues to rise while flow is decelerating or decreasing. Characteristic impedance (Zc) can be estimated as the first systolic shoulder, P1/peak flow, ΔQ. Aortic augmentation index (AIx) = AP/PP (1).

Figure 4.2A Aortic stiffness (carotid-femoral PWV)-related variation in central aortic and brachial pulse pressures (PP). As aortic stiffness increases both central (closed bars) and peripheral (open bars) PP increase but at different rates because of the influence of wave reflection on the central PP. In youth the aorta is compliant and the difference between peripheral and central PP is relatively large (18 mmHg); in old age the aorta is stiff and the difference is small (5.0 mmHg). Data were collected from 200 normal subjects ranging in age from 18 to 83 years. Over this life span P1 increased from 26 to 40 mmHg while AP increased from 0.0 to 18 mmHg.

Figure 4.2B Aortic stiffness-related variation in pulse pressure (PP) amplification (peripheral PP/central PP). As aortic stiffness (carotid-femoral PWV) increases amplification decreases (primarily because of the increase in wave reflection amplitude, AP). Data were collected from the same group of normal subjects as in Figure 2A. Amplification decreased from 1.7 to 1.1 over the life span studied (18 to 83 years).

Figure 4.3 The influence of wave reflections on invasively measured (multi-sensor catheter) ascending aortic pressure (P) and flow (Q) waveforms. The reflected pressure wave adds to the forward traveling wave by the superposition principle while the reflected flow wave subtracts from the forward traveling flow wave. Note that the forward pressure and flow waves are identical, as are the reflected waves, except that the reflected flow wave is inverted compared to the reflected pressure wave. P_i is the inflection point indicated on the pressure wave (1).

Figure 4.4 Non-invasive recordings of radial artery pressure waves (**left**) and synthesized (mathematical transfer function) aortic pressure waves (**right**) in three healthy individuals to illustrate the age-related changes in wave reflection characteristics, pressure wave shapes and PP amplification. Solid arrows identify the peak of the reflected waves from the lower body, and broken arrows indicate the beginning upstroke of the reflected waves on the aortic pressure waves. Advancing age and increased elastic artery stiffness cause the reflected wave to move from diastole where it is beneficial (increased coronary perfusion) to systole where it is detrimental (increased myocardial oxygen demand). During this process reflected wave amplitude increases from zero to 28 mm Hg in systole resulting in elevated LV load and wasted energy and a decrease in PP amplification (Amp). P1 is radial artery pulse pressure and P2 is the

reflected wave from the lower body (radial augmentation index =P2/radial P1) (1). Sp - systolic pressure; Dp – diastolic pressure; MP – mean pressure; PP – pulse pressure.

Figure 4.5 Illustration showing changes in the aortic pressure wave which occur during the development and progression of LV failure. A). Young normal healthy subject with reflected wave occurring predominately in diastole; ejection duration (broken line) is 316 ms, central PP is 26 mm Hg and SPTI is 2047 mm Hg sec/min. B). During aging and develop of hypertension the reflected wave (second shoulder, amplitude 23 mm Hg in this example) occurs almost entirely in systole resulting in an increase in AP, AIx, wasted energy, central PP (59 mm Hg) and SPTI (3206 mm Hg sec/min) causing LVH which begins the process of systolic heart failure. C). As heart failure proceeds reflected wave amplitude (7 mm Hg), AIx, central PP, ejection duration (269 ms) and SPTI (2196 mm Hg sec/min) begin to decrease. D). In severe LV failure, AP and wasted energy become almost zero, LV ejection is shortened further (235 ms) which causes a reduction in SPTI (1535 mm Hg sec/min) (352). HR – heart rate.

Figure 4.6 Measured radial artery and synthesized aortic pressure waves recorded in a heart failure patient (53 yo) before (top) and after heart transplantation (bottom). The failing LV could not generate enough force to overcome the mid-to-late systolic pressure boost usually seen at this age. This reduced contractile force resulted in an abbreviated ED (240 msec) and a low, AP and AIx. After heart transplant the LV could again generate the necessary force to overcome the mid-to-late systolic pressure boost which caused an increase in ED (309 msec), AP and AIx. Heart rate was similar before and after transplant (75 b/m) (352).

Figure 4.7 Measured radial artery and synthesized aortic pressure waves recorded in a normotensive patient at baseline and after sublingual nitroglycerin (0.3 mg). The drug caused a delay in transmission velocity of the reflected wave (Tr increased) from the lower body that resulted in a decline of augmented pressure, AP (from 15 to 3.0 mm Hg) and systolic duration. These changes caused a reduction in AIx and wasted LV and an increase in PP amplification. Aortic systolic pressure decreased 14 mm Hg, while brachial systolic pressure remained essentially unchanged (2.0 mm Hg).

Figure 4.8 Measured radial artery and synthesized aortic pressure waves recorded in a hypertensive patient at baseline and after four months treatment with the ACEI lisinopril (20 mg). The drug caused a delay in transmission velocity of the reflected wave (Tr increased) that resulted in a decline of augmented pressure, AP (from 24 to 8.0 mm Hg) and AIx (from 33% to 17%). Systolic duration of the reflected wave decreased (from 211 to 175 msec) causing a decline in wasted LV energy. Aortic systolic pressure (SP) decreased 36 mm Hg, while brachial systolic pressure was less sensitive, decreasing 25 mm Hg. Diastolic (DP) and mean (MP) pressure decreased by the same amount and PP amplification (Amp) increased from 1.1 to 1.4 (352).

Figure 4.1

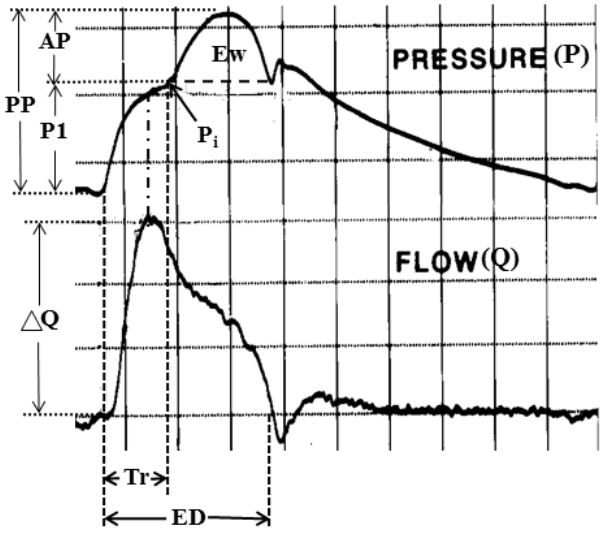


Figure 4.2A

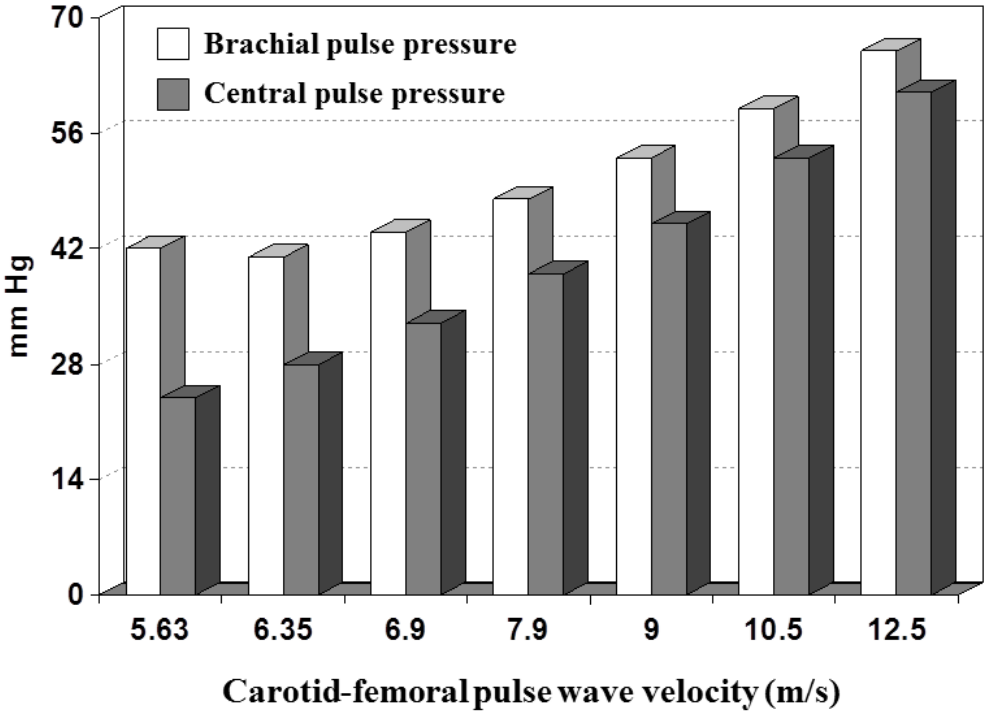


Figure 4.2B

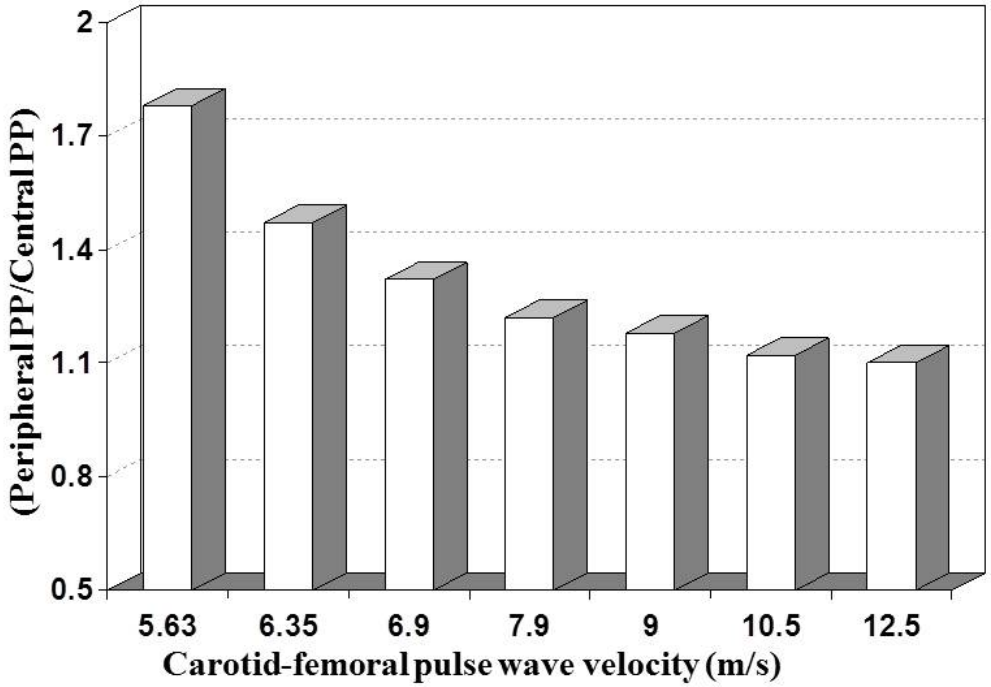


Figure 4.3

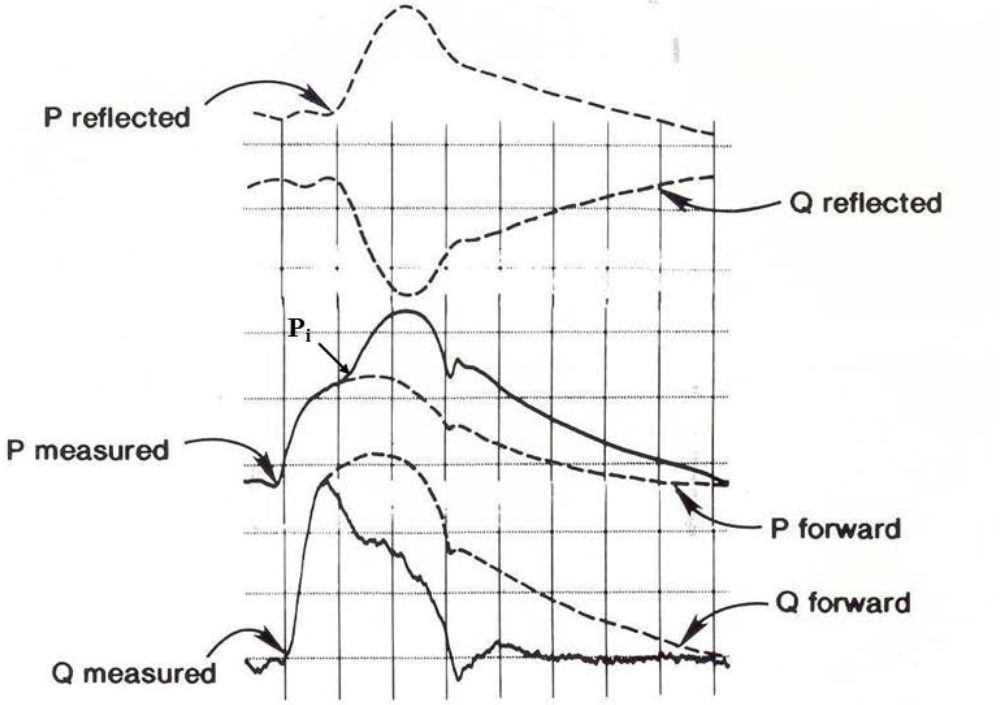


Figure 4.4

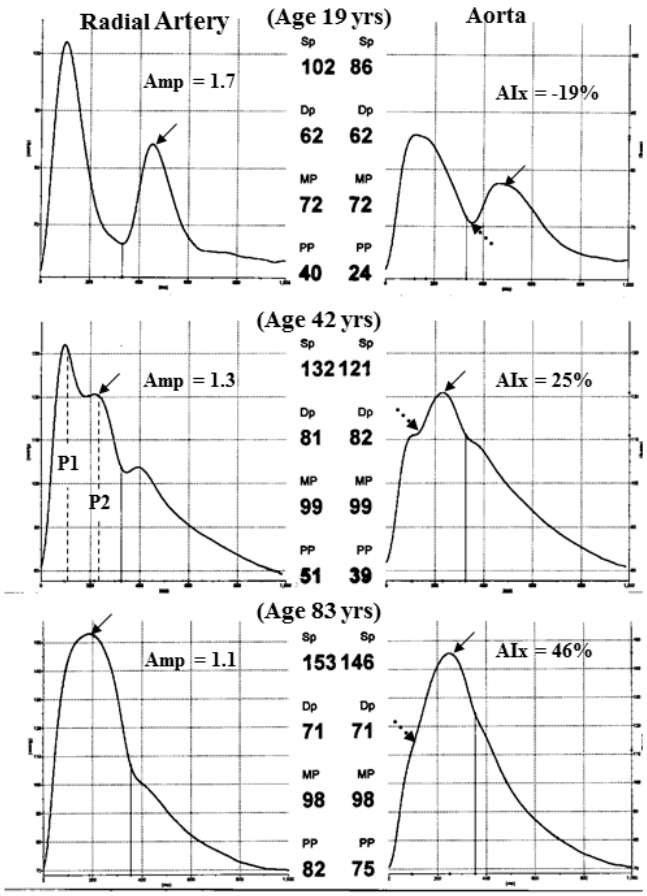


Figure 4.5

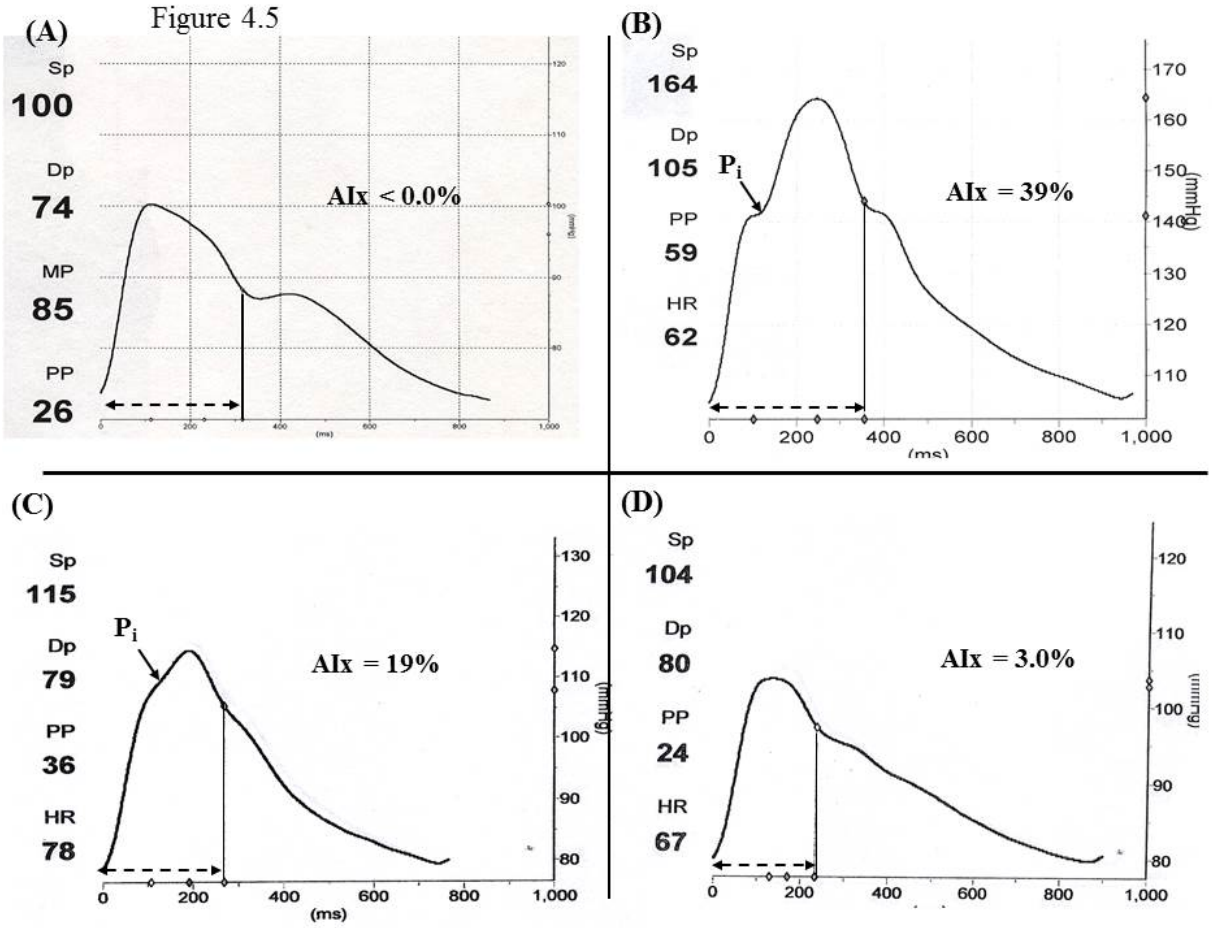


Figure 4.6

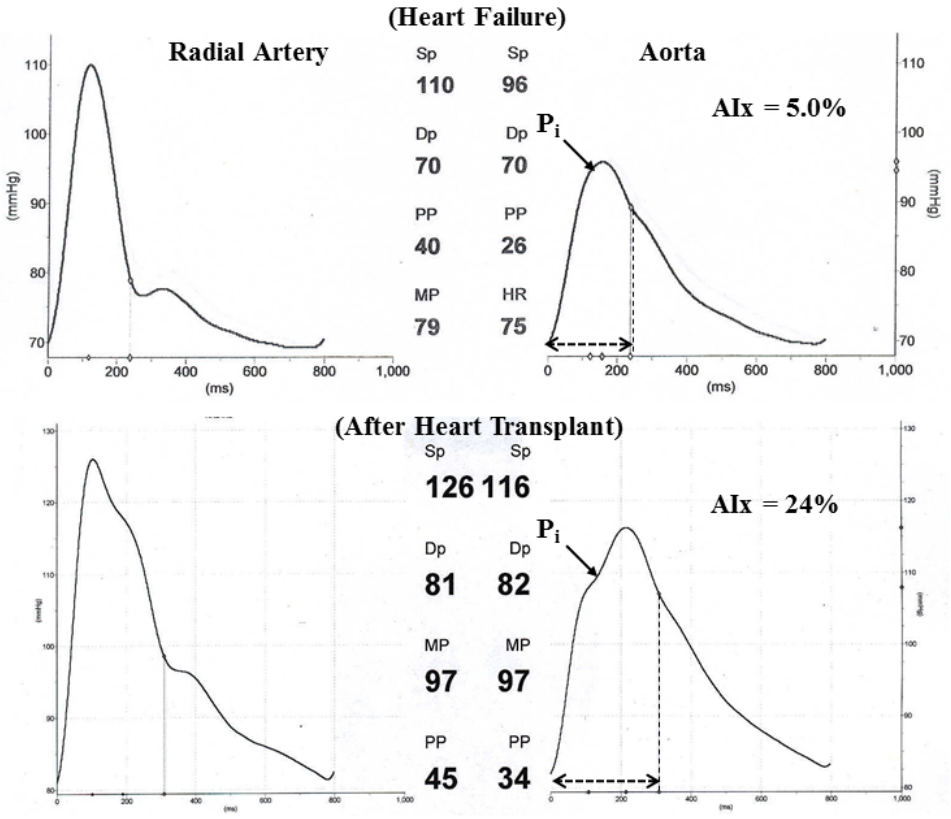


Figure 4.7

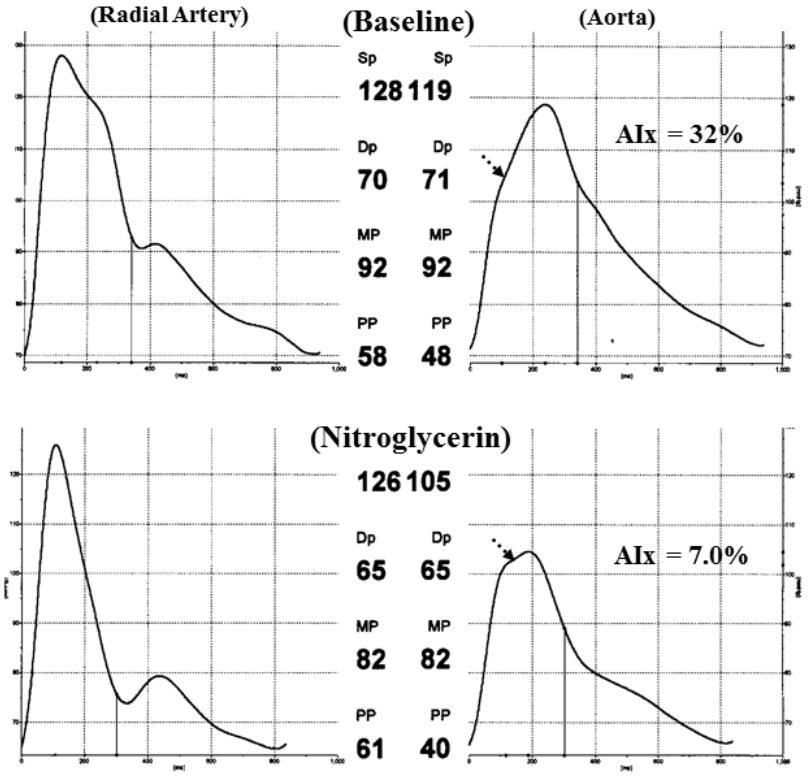
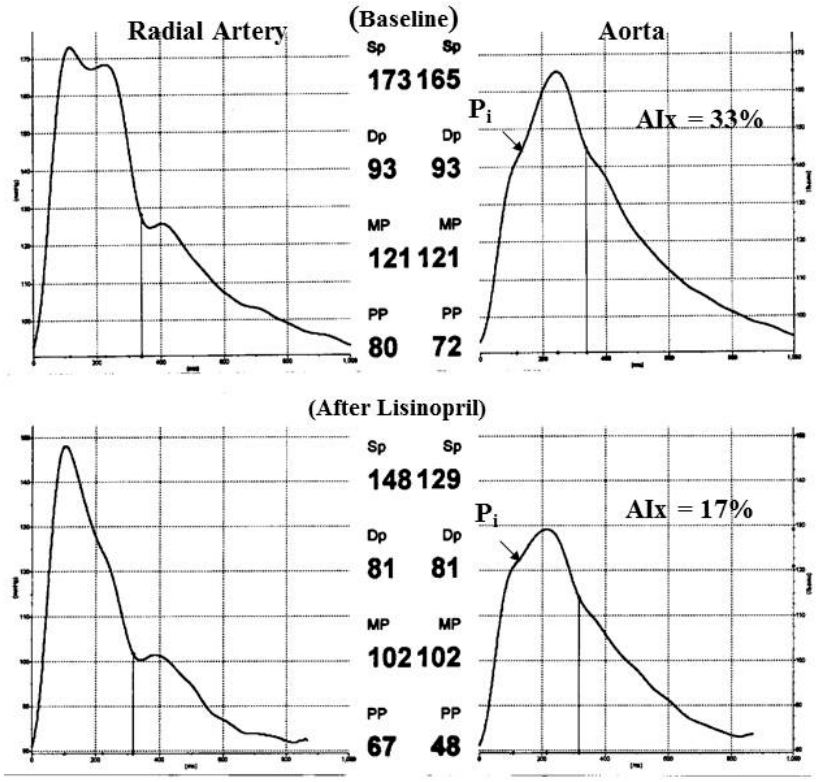


Figure 4.8



SECTION 5: Arterial stiffness in children

Authors: Elaine M. Urbina

Measures of arterial wall stiffness

Recent studies of arterial stiffness in youth published since the previous AHA statement on vascular assessment are summarized in Table 2 (635). The most commonly employed techniques are carotid ultrasound, echocardiogram for aortic stiffness and tonometry for large and small artery elasticity indices.

Global measures

Few Pediatric studies have evaluated global measures of arterial stiffness in children. Ahimastos et al (636) calculated systemic arterial compliance with a method combining Doppler and tonometery parameters. They found compliance was lower in pre-pubertal females but this gender difference was lost post puberty. Using impedance cardiography, one investigator found higher peripheral resistance index in white prehypertensive adolescents and higher cardiac index in blacks (637), the exact opposite relationship that was found in the Bogalusa Heart study with cardiac ultrasound measurements (638). Also using impedance cardiography, a relationship between lower birthweight and higher systemic vascular resistance after stress was found (639). Systemic vascular resistance measured with this technique improves in pre-hypertensive obese adolescents treated with treatment to lower uric acid levels (640). Higher pulse pressure/stroke volume ratio measured at age 11.5 years, which the authors stated reflected increased arterial stiffness, was related to smaller fetal size at 35 weeks (641). Using stroke volume/pulse pressure ratio as an estimate of whole body arterial compliance, another group found reduced compliance in very low birth weight premature infants at 7 weeks after birth also suggesting early programming influences later CV physiology (642). A few studies have also calculated arterial stiffness parameters from ambulatory BP recordings. The QKD interval is the time between the onset of ECG depolarization (Q) and detection of the last Korotkoff sound (K) at the brachial artery corresponding to DBP (d). Although it has not been validated against invasive measures of arterial stiffness, QKD is inversely correlated to PWV and other indices of arterial distensibility and left ventricular function (643). Using this technique, children operated on for

Cushing's syndrome (644) had abnormal values as did patients with Williams syndrome (645), suggesting increased arterial stiffness as an etiology for the high prevalence of hypertension in these patients. Adolescents who had been operated upon for acromegaly also had higher QKD compared to controls (646). The ambulatory arterial stiffness index (AASI) is calculated as 1 minus the slope of the regression of DBP on SBP from 24-hour ambulatory BP data. Arterial stiffness measured by AASI was elevated in children with hypertension (647), especially if due to aortic coarctation (648). AASI was also elevated in children with type 1 diabetes mellitus if they had hypertension or white coat hypertension (649). However, it should be noted that AASI may represent ventricular-arterial coupling rather than arterial stiffness per se (181).

Hybrid indices

Augmentation index (AIx), which combines features of wave reflection and arterial stiffness, is finding increasing use in pediatric research. In contrast to PWV where most studies had similar findings, the results relating AIx to CV risk factors and high risk disease states is less clear. Some disparities may be accounted for by differences in height which is a major determinant (650). Early programming may influence later AIx as there was a negative correlation between birth weight and AIx measured in their mothers (651) and AIx is higher in preterm children (652;653) and those exposed to antenatal steroids (654). However, the relationship between birth weight and AIx in men was lost after adjustment for adult height (655) and adolescent offspring of mothers with gestational diabetes had no difference in AIx compared to controls (656). Therefore, it is not clear if early programming has a profound effect on wave reflections measured later in life.

There is a more robust relationship between AIx and CV risk factors. Young adults with a family history of hypertension were found to have higher AIx than subjects with a negative history independently of their current BP (657). When subjects were stratified as normo-, pre- or true-hypertensives in one large study of 723 adolescents and young adults, there was a graded increase in AIx across the BP strata (658) although this relationship was not found is a similar size European study (659). Higher AIx has also been found in children with familial hypercholesterolemia (660), obesity (661;662), poor glucose handling (663), insulin resistance (664), poor self-esteem (665), low serum vitamin D (666), and obesity-related risk factor

clustering (667). Adverse health habits such as inactivity (668;669), or poor diet (670) have also been found to lead to higher AIx.

Limited studies have also been performed in children with renal disease, congenital heart disease, and diabetes. Pediatric dialysis patients had significantly higher AIx than controls (671) but unfortunately this may not improve after kidney transplantation (672). Patients with a 'gothic-type' aortic arch after coarctation repair were found to have elevated Aix (673), as were patients with Marfan syndrome (674), and repaired tetralogy Fallot where AIx correlated with the sinotubular junction z-score (675). These results suggest increased stiffness may be involved in late aortic complications seen in these lesions. The most data is available evaluating AIx in youth with diabetes (676-679). Many investigators have found higher AIx in pediatric patients with type 1 (680-684), and type 2 diabetes mellitus (661;685), with type 2 diabetics demonstrating higher values even with shorter duration of disease (686). The one study that found no difference was substantially smaller (only 45 cases and 42 controls) (687). Similarly, a longitudinal study that did not see an increase in AIx in youth with diabetes over 2.5 year studied only 18 subjects (688).

Even less data is available regarding small and large artery elasticity index in children. Two studies found lower large artery elasticity index with low birthweight (689;690), and one found higher systemic vascular resistance measured with the same tonometry device was associated with higher maternal cortisol levels although no mention was made of the elasticity indices that are measured simultaneously with the SVR (691). Normotensive male adolescents and adults (16-30 years) with a family history of HTN had lower small and large artery elasticity index but no relationship was found in females (692). Physical activity was related to small artery elasticity index in children age 8 to 11 years (693). There was no difference in elasticity between healthy adolescents and those with type 1 diabetes but there was a direct relationship between small artery elasticity and body weight status in one (694). Conversely, another study found paradoxically greater small and large artery elasticity index in obese children age 8 to 18 years (695) suggesting that these indices may not be as robustly related to CV risk factors in children and adolescents as some other measures of arterial stiffness.

Technical considerations in measurement in children

For specific recommendations on measurement techniques reference should be made to the previous AHA paper on non-invasive measures in children (635).

Measures of pulse propagation

The major technical considerations are similar to issues faced when measuring PWV in adults. One issue is the lack of equivalence of results using different techniques such as Doppler, tonometry, magnetic resonance imaging, photo- or volume-plethysmography or oscillometric pressure cuffs (See Table 5.1). These techniques may use different algorithms for identifying the point on the tracing used to define the "foot' of the waveform. There are also variations in technique for measuring proximal to distal pulse propagation distance (696). The volume plethysmography method for assessing baPWV uses a proprietary algorithm for estimating arterial path length that was validated in a Japanese population. It is not clear that this algorithm is applicable to all races/ethnicities as baPWV values are substantially different in American and Japanese adolescents (697). These differences make comparisons among techniques impossible even when the underlying technique is similar (i.e. two devices that use tonometery to measure carotid femoral may not produce equivalent PWV). Bland-Altman comparisons were made between cfPWV measured in adolescents with a new oscillometric technique and two tonometric devices (698). Although there was excellent agreement, the oscillometric technique demonstrated a small but significantly lower PWV at higher PWV values (698). Also, PWV along the aortic path cannot be compared to the higher PWV measured in the smaller peripheral (arm and leg) blood vessels. Separate normal values for each artery need to be used.

Other issues encountered in pediatrics are difficulty in obtaining complete applanation of an artery in younger subjects, inability of children to lay still and lack of appropriate cuff sizes for devices that employ them. However, despite these limitations, studies of pulse wave propagation have been published even in toddlers (699) and newborns (700). Reproducibility has not been a major issue with PWV measurements in pediatrics with quality control calculations demonstrated coefficient of variability for tonometry based readings of less than 7% (661).

Measures of arterial wall stiffness

High quality images of the common carotid artery are routinely obtained from older children and adolescents with coefficients of variability ranging from 5.3 to 8% (701). Obtaining images for

either B-mode or B-mode guided M-mode of the common carotid artery in younger children may be more challenging as the changes in arterial diameter in some studies are measured in hundredths of a millimeter (702-704). If adequate images can be obtained, sonographers should be instructed to use the lightest pressure possible in obtaining the image so as not to obscure the natural pulsations of the vessel. An alternative approach is ultrasound imaging of the abdominal aorta where intima-medial thickness has been measured successfully in neonates (705), although few studies have used these abdominal aorta images to calculate arterial stiffness in children (706).

The non-ultrasound method for measurement of brachial artery distensibility has demonstrated excellent reproducibility with coefficients of variability less than 10% (661). Reproducibility of other measures of arterial wall stiffness in children, and the minimum age at which these values can be obtained, have not been established.

Hybrid indices

The major technical limitation in measurement of hybrid indices in children relate to inability to achieve acceptable applanation of the smaller arteries in younger children. Devices which have a tonometer in a rigid housing may not be able to achieve high quality waveforms although investigators have successfully applied both hand held (680) and device held tonometers (690) in children as young as 5 years of age. Reproducibility of pulse wave form analysis may not be as high as with PWV, however, investigators have published intra-class correlation coefficients between 0.7 and 0.9 when obtained in adolescents (661). As with other measures of arterial stiffness, values obtained in children with different devices are not equivalent as augmentation index measured with fingertip tonometry was found to be significantly different from radial tonometry (707).

Another challenge in obtaining high quality measures of augmentation index is the higher degree of respiratory sinus arrhythmia in children. Some subjects may therefore have highly irregular pulse making it difficult to obtain 10 seconds of steady wave form data.

Developmental changes in arterial function in childhood

Many investigators have found an increase in arterial stiffness from childhood to adolescence (97;708-710)**,** including large and small artery compliance (711). Using MRI, Voges found a decrease in descending aorta distensibility and increase in PWV starting at age 2.3 years (712). It appears this must relate to changes in the vessel wall since vascular compliance is determined by both vessel size and distensibility of the wall and the MRI study demonstrated a steady increase in cross sectional area of the descending aorta (with a slight plateauing after 15 years of age (712). Similarly, Senzaki found that although arterial compliance increased from birth to 20 years, once normalized for BSA 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 (713). Whether there are gender-related differences in developmental changes in arterial stiffness is less clear as Ahimastos found lower systemic arterial compliance and PWV in pre-pubertal girls compared to boys with no difference seen post-puberty (714), Fischer found sex differences in PWV both pre- and post-puberty (709), and Voges found no difference (712). 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.

Gaps in Knowledge:

1. Lack of validation:

While the measurement of PWV has become the leading modality for assessment of arterial stiffness in pediatric populations, no validation studies for any of the PWV techniques have been performed in youth. However, there is no reason to believe that the experiments proving simultaneous non-invasive measurements of PWV correlated with intra-arterial measurements in adults would not apply equally to children. Furthermore, it would be unethical to subject healthy children to such invasive testing for the sole purpose of a validation study. Additionally, one study in children did measure PWV during invasive cardiac catheterization and they obtained values similar to those produced with non-invasive devices (715) suggesting the validity of the technique in children.

The non-ultrasound method for evaluating brachial artery distensibility has been validated in adults demonstrating excellent correlation between measurements obtained during cardiac catheterization (r = 0.83) (716) but this device has not been validated in children. However, there

are no assumptions used in the model used to calculate brachial artery compliance (716) that would be invalid in children. However, it is not known if the algorithm used to estimate baseline brachial artery diameter from gender, height, weight, and mean arterial BP, which was validated using B-mode ultrasound in adults ($n = 1,250$, $R = 0.63$, $p \leq 0.05$) (635) will apply equally well to children. Since distensibility is compliance normalized to baseline diameter, if the diameter estimation is faulty, erroneous values could result.

As with other measures of arterial stiffness, no validation experiments have been performed on global measures of arterial stiffness. However, the underlying models relating these non-invasive measures to invasive measures of arterial stiffness in adults should be valid in children. Although no validation of large and small artery elasticity index have been performed, a small number of children (N=12, 3-18 years) have participated in a study replicating adult validation studies for AIx (717). Children undergoing catheterization for atrial septal defect closure had measurement of pressure wave forms at the ascending aorta with a pressure-type catheter with simultaneous radial artery pressure curves obtained with tonometry. Fast Fourier analyses resulted in a transfer function with the same peak at the fourth harmonic (717) as demonstrate by O'Rourke et al (718), suggesting the validity of this technique in children of different sizes and heart rates.

2. Lack of sufficient normative data by age, body size, pubertal status, gender, and race:

A few large epidemiologic studies defining normal values for PWV have included children (97;204;719;720), however, each had a small sample size for pediatric subjects. Likewise, many pediatric studies using PWV have included small numbers of healthy control subjects (see Table 5.1). There are now a number of studies that have published data on larger numbers of healthy youth (see Table 5.3). Furthermore, although some larger studies have sufficient numbers to stratify by age, gender and race, covariates known to influence PWV in children, there is lack of consistency among techniques so the 'normal' values must be interpreted only for the specific device used.

When measuring arterial stiffness by calculations that use change in arterial diameter through the cardiac cycle in the calculations, one must be aware that there is a paucity of data examining the effects growth on arterial size and a lack of normative data on youth with a wide range of body sizes.

The only paper purporting to describe normative data on global measures of arterial stiffness in youth measured pulse pressure as a surrogate for arterial stiffness. In this longitudinal cohort of healthy youth in Minnesota, pulse pressure was evaluated over multiple visits and gender and race differences were explored (721).

A few studies with over 100 healthy controls age 20 or less have published normal values for AIx (Table 5.4). No normative data on small and large artery elasticity data in pediatric patients is available.

3. Lack of longitudinal data in healthy youth

Little is known about normal vascular aging across childhood and adolescence. One study did repeat PWV in 3 years and they found the increase was greater in males (0.79 $\pm$ 0.79 m/sec) than in females (0.27 $\pm$ 0.089 m/sec, $p \leq 0.0001$) (722). They also found that adolescents who reported lower physical activity had higher PWV at follow-up (722). More studies are needed to elucidate the determinants of accelerated vascular aging in youth.

4. Data in high risk conditions

While many studies using arterial stiffness in high risk youth have been published in the last few years, many disease processes are represented by small numbers of subjects and there is a lack of longitudinal data.

5. Effect of intervention

Few studies have evaluated arterial stiffness with an intervention. One small study of 15 subjects found no improvement in PWV after renal transplant (723). A randomized trial of 25-hydroxyvitamin D administration in 49 adolescents aged 16 $\pm$ 1.4 years demonstrated an increase in PWV over the 16 week intervention in the control group (5.38 $\pm$ 0.53 to 5.71 $\pm$ 0.5 m/sec) with a decrease in PWV in the treatment group (5.41 $\pm$ 0.73 to 5.33 $\pm$ 0.79, $p \leq 0.031$) (724). Clearly, more and larger trials assessing the utility of interventions in improving arterial stiffness in youth are needed.

One study administered atorvastatin to young patients with type 1 diabetics. They found a trend towards decrease in AIx after 12 weeks of treatment (-2.0 ± 7.0. $p = 0.06$) in this small sample of only 45 subjects age 10 to 21 years (725).

6. Lack of sufficient correlations to well established pediatric intermediate target organ endpoints.

A few pediatric studies have correlated arterial stiffness with evidence of CV risk factor-related target organ damage such as increased carotid intima-media thickness (680;726;727). More importantly, pediatric data is now available relating arterial stiffness measures to LV mass (728;729). Urbina et al (717), combined stiffness measured at the carotid artery with peripheral measures including PWV, brachial artery distensibility and augmentation index into a global stiffness index. This index demonstrated a linear relationship with LVM and global stiffness index as an independent determinant of LVM even after adjusting for other CV risk factors (717). Similar to findings in adults (730), these data demonstrate the adverse effects of increased arterial stiffness and portend a less advantageous cardiac future. Data relating stiffness to other forms of target organ damage such as microalbuminuria, retinopathy, cognitive decline or neuropathy are lacking in pediatric patients.

Table 5.1.Studies of PWV measured in childhood

Author, Year	PWV Method†	Population, average age	Number	Results
Ahimastos, 2003 (636)	C-F, F-D, tonometry	Pre-pubertal, 10 years, post-pubertal, 16 years	N = 58 pre-, N= 55 post-pubertal	C-F & F-D higher in females pre-pubertal, C-F same post-pubertal, F-D higher males post-pubertal
Aoun, 2010 (723)	C-F, tonometry	Children on hemodialysis, 11 years	N = 15	PWV did not decline after renal transplant
Arnberg, 2012 (668)	C-F, tonometry	Obese children, 13 years	N = 183	PWV lower in association with higher milk intake
Biglino, 2012 (731)	Thoracic aorta, MRI	Children after HLHS repair, 3-5 years	N = 10, 11 controls	PWV higher in patients after HLHS repair
Briese, 2008 (672)	C-F, tonometry	Children with renal transplant, 14 years	N = 36 cases, 49 controls	PWV higher with renal transplant
Buehler, 2012 (732)	C-F, photo plethysmography	Children with cystic fibrosis, 12 years	N = 31, 48 controls	Trend for higher PWV in patients
Canpolat, 2013 (733)	C-thigh, volume displacement	Children with SLE, 14 years	N = 24 cases, 36 controls	Patients had significantly higher PWV than healthy controls
Celik, 2011 (734)	Doppler, Aorta from valve to diaphragm	Obese children, 13 years	N = 30 cases, 30 controls	PWV higher in obese
Charakida, 2009 (735)	C-R, tonometry	Children with HIV, 11 years	N = 83 cases, 59 controls	PWV higher in HIV
Chen, 2012 (722)	C-F (assumed), Tonometry	Adolescents, 17 years	N = 162	PWV increase over 3 years greater in males and subjects with decreased physical activity
Cheung, 2002 (736)	B-R, photo-	Children with	N = 13 cases, 155	PWV higher with vasculitis

	plethysmography	polyarteritis nodosa, 12 years	controls	
Cheung, 2004 (737)	B-R, photo-plethysmography	Children with Kawasaki disease, 9 years	N = 66 cases, 36 controls	PWV higher in Kawasaki disease
Cheung, 2006 (675)	H-F, F-A, tonometry	Children after tetralogy of Fallot repair	N = 31 cases, 31 controls	PWV higher after tetralogy of Fallot repair
Covic, 2006 (671)	C-F, tonometry	Children on hemodialysis age 14 years	N = 14 cases, 15 controls	PWV higher in children on hemodialysis
Cseprekal, 2009 (738)	C-F, tonometry	Children after renal transplant, 15 years	N = 25 cases, 75 controls	PWV z-score higher after renal transplant
Dangardt (739)	C-R, tonometry	Adolescents, 14 years	N = 30 cases, 18 controls	PWV lower in obese but measured only C-R
De Divitiis, 2003 (740)	B-R, photo-plethysmography	Children & adults after coarctation repair, 9-58 years	N = 72 cases, 53 controls	PWV higher after coarctation repair
Detchaporn, 2012 (741)	A-F, photoplethys-mography	Children iwht thalassemia, 14 years	N = 30, 30 controls	Thalassemia patients have higher PWV
Dietz, 2011 (742)	C-F, Doppler probes	Adolescents, 16-21 years	N = 157	PWV higher with severe depression
Dursun, 2009 (743)	C-F, Doppler	Youth with renal disease, 11-15 years	N = 70 cases, 18 controls	PWV higher in youth with renal disease
Edwards, 2012 (669)	C-F, tonometry	Youth, 10-23 years	N = 548	PWV higher with lower physical activity
Gerhard-Herman, 2012 (744)	C-F, Echo Doppler	Youth with progeria, 3-16 years	N = 26 cases, 62 controls	PWV higher in patients with progeria
Gordon, 2013 (745)	C-F, tonometry	Males who were lean, obese or	N = 9 lean, 11 obese, 10 T2DM	Subjects with T2D had lower phospholipid content in large HDL particles that was

		T2DM, age 16-23 years		inversely associatedwith PWV. No association with HDL-C
Grotenhuis, 2008 (746)	AA-AD, AD-I, MRI	Youth after transposition of great arteries repair, 16 years	N = 15 cases, 15 controls	PWV higher after transposition of great arteries repair
Harris, 2012 (747)	Thoracic aorta, Echo Doppler	Obese age 14 years	N = 61 cases, 55 controls	PWV higher in obese
Heilman, 2009 (680)	C-F, tonometry	Children with type 1 diabetes, 5-18 years	N = 30 cases, 30 controls	PWV correlated with diabetes duration. Trend for higher PWV
Herceg-Cavrak, 2011 (748)	H-I, oscillometry	Children after anthracyclines for cancer age 6-20 years	N = 53 cases, 45 controls	PWV higher after anthracyclines
Hussain, 2012 (749)	MRI along thoracic aorta	Adolescents after heart transplant, 16 years	N = 10	PWV higher than published normals, correlated with coronary artery vasculopathy on IVUS
Im, 2007 (750)	B-A, volume plethysmography	Adolescents, 12-18 years	N = 262	PWV higher in males, determinants sex, MAP, BMI, homocysteine
Kenny, 2011 (657)	H-L, oscillometric	Youth after coarctation repair, 16 years	N = 29 cases, 20 controls	PWV higher after coarctation repair with hypertension
Khadikar, 2012 (751)	Ultrasound for local PWV along carotid	Indian children 11.4 years	N = 140 overweight/ obese, 60 controls	PWV higher in children with metabolic syndrome whose parents also have metabolic syndrome than in children with metabolic syndrome from normal parents
Kis, 2008 (752)	C-F, tonometry	Children on dialysis, 14 years	N = 11 cases, 133 controls	PWV higher on dialysis
Klinge, 2009 (753)	C-F, C-Ft, C-R, tonometry	Children after cardiac transplant, 13 years	N = 22 cases, 95 controls	PWV higher after cardiac transplant

Koopman, 2012 (754)	C-F, tonometry	Children with obesity, age 14 years	N = 21, 27 controls	PWV higher in obese children
Kotsis, 2011 (755)	C-F, tonometry	Healthy subjects, 21 years	N = 115	Independent determinants age, 24-hr SBP variability.
Koudsi, 2007 (700)	SSN-Ao, infra-red and ultrasound probes	Neonates, 1-3 days	N = 148	PWV lower with higher maternal BP at 28 weeks gestation.
Kucerova, 2006 (756)	C-F, tonometry	Young adults, 24 years	N = 174	PWV higher in offspring of hypertensive parents,but disappeared with adjustment for age and MAP
Kwok, 2003 (757)	B-R, photoplethysmography	Children with primary snoring, 9-10 years	N = 30 cases, 30 controls	PWV higher in children with primary snoring
Kyvelou, 2010 (758)	C-F, tonometry	Young adults, 24 years	N = 88 cases, 55 controls	PWV higher in offspring with parental history of hypertension independent of BP
Lee, 2007 (759)	B-A, volume plethysmography	Male adolescents, 12-18 years	N = 256	PWV independently correlated with insulin resistance
Lurbe, 2012 (760)	C-F, tonometry	Youth, 8-18 years	N = 501	PWV showed graded increase across BP strata
Madhura, 2012 (761)	Brachial-finger, photo plethysmography	Young adults 18-25 years	N = 18	PWV is lowered after 8 weeks aerobic exercise
McEniery, 2011 (652)	C-F, tonometry	Adolescents with prematurity vs controls	N = 68 cases, 90 controls	No difference
Midei, 2009 (762)	C-F, Doppler probes	Adolescents	N = 160	PWV higher with higher attachment anxiety & hostility
Miyai, 2009 (763)	B-A, volume plethysmography	Adolescents, 15-17 years	N = 754	PWV independently determined by age, BP, insulin resistance

Morley, 2010 (764)	C-F, F-D, tonometery	Children, 9 years	N= 147 twin pairs	PWV higher in offspring of mothers reporting 2nd trimester alcohol consumption
Niboshi, 2006 (710)	B-A, volume plethysmography	Children, 10-18 years	N = 970	PWV higher in boys, increased with age, BP, HR.
Otsuki, 2007 (765)	C-F (assumed), tonometry	Athletes, 20 years	N = 35	PWV lower with longer duration of exercise training
Ou, 2008 (728)	AA-AD, MRI	Children after coarctation repair, 12 years	N = 40 cases, 20 controls	PWV higher after coarctation repair
Ou, 2008 (673)	AA-AD, MRI	Children after coarctation repair, 16 years	N = 55 cases, 20 controls	PWV higher after coarctation repair in Gothic vs. Romanesque arch shape
Pandit, 2011 (766)	Unspecified, ultrasound	Youth, 6-17 years	N = 139 cases, 69 controls	PWV higher in obese
Payne, 2007 (674)	C-F, tonometry	Marfan syndrome, 26 years	N = 10 cases, 10 controls	PWV no different in in this small study
Pierce, 2013 (767)	C-F, C-R, tonometry	African-American Adolescents, 16.9 years	N = 227	CF-PWV was 7% higher in overweight or obese than in lean subjects
Riggio, 2010 (660)	Calculated from Carotid Beta Stiffness Index from Ultrasound	Children with dyslipidemia, 11 years	N = 44 cases, 18 controls	PWV higher in familial hypercholesterolemia
Rodrigues, 2011 (768)	C-F, tonometry	Down syndrome, 13-42 years	N = 41 cases, 41 controls	PWV lower in Down syndrome, but disappeared after SBP adjustment
Roegel, 1998 (769)	C-F, tonometry	Young adults after coarctation repair, 21 years	N = 45 cases	PWV lower after coarctation repairbut ‘normal’ defined in Chinese population using Doppler method
Rossi, 2011 (770)	C-R, tonometry	Adolescents, 13-14 years	N = 49 cases, 41 controls	PWV higher with low birth weight due to pre-term birth, but not with small for gestational age.

Saiki, 2012 (771)	Proximal & Distal Aorta, micromanometer	Patients after tetralogy of Fallot repair	N = 98 cases, 63 controls	PWV higherafter tetralogy of Fallot repair
Sakuragi, 2009 (772)	C-F, tonometry	Children, 10 years	N = 573	PWV has negative correlation with fitness and positive correlation with BMI
Salvi, 2012 (773)	C-F, C-R, tonometry	Adolescents 16-20 years	N = 558	No relation of PWV to birth weight. Higher C-R PWV with accelerated growth in 1st year of life
Sarkola, 2011 (774)	C-F, C-R, F-D, tonometry	Youth after coarctation repair, 16 years	N = 36 cases, 37 controls	PWV higher for F-D only, after coarctation repair
Scherrer, 2012 (775)	C-F, tonometry	Children 11-12 years conceived with assisted reproductive technology	N = 65 cases, 57 controls	PWV higher after assisted reproductive technology
Segers, 2006 (776)	AA-AD, MRI	Marfan syndrome, 13-54 years	N = 26 cases, 26 controls	PWV higher with Marfan syndrome
Seki, 2012 (715)	Cardiac catheterization	Children after tetralogy of Fallot repair	N = 37 cases, 57 controls	PWV higher after tetralogy of Fallot repair
Shah, 2011 (667)	C-F, tonometry	Adolescents, 10-23 years	N = 474	PWV higher with clusters of CV risk factors
Shah, 2012 (685)	C-F, tonometry	T2DM, 10-23 years	N = 215	PWV higher in African-Americans higher with T2DM
Shah, 2012 (777)	C-F, tonometry	Adolescents with T1DM, 15 years	N = 225	Adiponectin is not an independent determinant of PWV in youth with T1DM
Shah, 2012 (685)	C-F, tonometry	Young adults with T2DM	N = 215	African-American young adults with T2DM have higher PWV than Caucasian patients
Stella, 1984 (778)	F-Ft, Doppler	T1DM, 2-19 years	N = 28 cases, 28 controls	PWV higher in T1DM
Song, 2012 (779)	Pulse transit	Obese boys	N = 22	Subjects who underwent aerobic exercise had

	time, tonometry			improvement in arterial stiffness
Tam, 2012 (656)	C-F, tonometry	Adolescents of mothers with gestational DM	N = 42 cases, 87 controls	PWV no different in case vs. control , but higher with higher umbilical cord C-peptide
Tawadrous, 2012 (780)	C-F, tonometry	Adolescents with chronic kidney disease	N = 15 dialysis, 14 transplant, 15 controls	PWV higher than controls for dialysis patients, no difference for transplant patients
Tedesco, 2000 (781) and 2001 (782)	C-F, tonometry	Neurofibromatosis type 1, 12 years	N = 64 cases, 30 controls	PWV no different
Thurston 2009 (783)	C-F, Doppler probes	Adolescents, 18 years	N = 159	PWV different in different racial groups
Urbina, 2010 (681)	C-F, tonometry	T1DM, 15-18 years	N = 535 cases, 241 controls	PWV higher with T1DM after age-adjusted
Urbina, 2010 (661)	C-F, tonometry	Youth, 10-23 years	N = 670	PWV higher in graded fashion from lean to obese to T2DM
Urbina, 2011 (658)	C-F, tonometry	Youth, 10-23 years	N = 723	PWV higher in graded fashion across BP strata
Urbina, 2012 (664)	C-F, tonometry	Adolescents and young adults, 15-28 years	N = 343	Higher PWV seen in obese subjects with insulin resistance as compared to obese non-insulin resistant or controls
Urbina, 2013 (784)	C-F, tonometry	Youth, 10-26 years	N = 894	PWV higher in graded fashion across tertiles of TG/HDL ratio
Voges, 2013 (785)	MRI, thoracic aorta	Young patients after arterial switch operation 6-31 years	N = 51, 34 controls	PWV higher in adult patients compared to controls but no difference in young patients
Wadwa, 2010 (686)	C-F, tonometry	Youth DM, 10-23 years	N = 535 T1DM, 60 T2DM	PWV higher in T2DM vs. T1DM related to CVRF
Walker, 2013 (786)	C-R, tonometry	Youth, 12.5 years	N = 485	No relations between cardiometabolic risk factors and C-R PWV in healthy, lean subjects
Van de Laar, 2011(787)	A-I, A-R, A-D, photoplethysmo grapy	Smoking at 15 years, PWV at 23 years	N = 424	PWV higher for A-I only with smoking
Yildiz, 2009 (788)	C-F, tonometry	Adolescents and	N = 29	PWV higher in the morning, negative

		young adults, 18-27 years		correlation with melatonin
Yildiz, 2010 (789)	C-F, tonometry	Children with epilepsy on medication	N = 59 cases, 23 controls	PWV higher if on carbameqepine & valproate
Yu, 2011 (790)	B-A, volume plethysmography	Children with glomerulonephritis, 10 years	N = 11 cases, 25 controls	PWV higher in cases but improves with disease abatement
Yu, 2012 (791)	B-A, volume plethysmography	Children with T1DM	N = 87 cases, 21 controls	No difference in baPWV between diabetics and controls
Zhu, 2007 (637)	C-R, C-Ft, tonometry	Adolescents, 18 years	N = 942	PWV higher in whites with pre-hypertension
Zhu, 2008 (792)	C-R, C-Ft, tonometry	Adolescents, 17-18 years	N = 702	PWV higher in association with adhesion molecule gene polymorphism PWV
Zhu, 2008 (793)	C-R, C-Ft, tonometry	Adolescents, 17-18 years	N = 972	PWV higher in obese vs. lean

†AA-AD = ascending aorta -proximal descending aorta AD-I = proximal descending aorta-abdominal aorta proximal to iliac bifurcation, A-D = aorto-dorsalis pedis, A-I = aorto-iliac, A-R = aorto-radial,B-A = brachial ankle, B-R = brachial radial , C-F = carotid-femoral, C-Ft = carotid-foot, C-R = carotid-radial, F-A = femoral-ankle, F-D = femoral-dorsalis pedis, H-F = heart-femoral, H-I = heart-iliac bifurcation, H-L = heart-leg, SSN-Ao = supra sternal notch-abdominal aorta

Table 5.2. Recent studies of Arterial Wall Stiffness in childhood

Author, Year	Measure	Results
Banach, 2010 (794)	Carotid ultrasound	Overweight children have stiffer carotid
Donato Aquaro, 2011 (795)	MRI for aortic distenstion	Distension is lower in adolescents with bicuspid aortic valve
Evelein, 2012 (796)	Carotid ultrasound	Is higher in children whose parents have higher BP
Evengul, 2012 (797)	Echo for aortic stiffness	Adolescent and young adult offspring of hypertensive parents have higher aortic stiffness
Ferreira, 2012 (798)	Carotid ultrasound	Adolescents with elevated CV risk factors have higher carotid stiffness at age 36 years
Galler, 2010 (799)	Carotid ultrasound	Children with T1DM have increased aortic stiffness
Gardner, 2013 (800)	Small and large artery elasticity index	No difference in elasticity between youth with or without metabolic syndrome
Geerts, 2012 (801)	Carotid ultrasound	Obese children have stiffer carotid
Geerts, 2012 (802)	Carotid ultrasound	Children of mothers who smoked during pregnancy had less distensible carotid
Harris, 2012 (747)	Carotid ultrasound	Excess early postnatal weight gain leads to stiffer carotid
Holmquist, 2012 (803)	Carotid ultrasound	Elasticity is lower in youth with T1DM with lower levels of urine excretion of glutathinone S-transferase
Iannuzzi, 2010 (804)	Carotid ultrasound	Children living near main highways had stiffer carotid
Iwashima, 2011 (805)	Carotid ultrasound	Adiposity correlates with carotid stiffness
Jin, 2013 (806)	Carotid ultrasound	Obese youth have stiffer carotid
Maurice, 2012 (807)	Echo for aortic stiffness	Aortic stiffness is higher after Kawasaki disease

Nettlefold, 2012 (693)	Small and large artery elasticity index	Physical activity is related to small but not large artery elasticity in healthy children
Oliviero, 2010 (808)	Ultrasound for brachial distensibility	Congenital hypothyroid patients had lower distensibility
Oyamada, 2012 (809)	Echo for aortic stiffness	Children with Kawasaki disease have altered elastic properties compared to controls
Ozari, 2012 (810)	Carotid resistance index from Doppler	Resistance index is higher in young adult males who are obese
Ozecetin, 2012 (811)	Carotid ultrasound	Carotid stiffness is higher in obese children
Pac, 2010 (812)	Echo for aortic stiffness	Aortic stiffness is higher in obese children
Pandit, 2011 (766)	Carotid ultrasound	Carotid stiffness is higher in obese children
Pees, 2012 (813)	Echo for aortic stiffness	Children with bicuspid aortic valve have stiffer aorta
Santarpia, 2012 (814)	Echo for aortic stiffness	Bicuspid aortic valve is associated with higher aortic stiffness
Strambi, 2012 (815)	Small and large artery elasticity index	Elasticity is impaired in children and adolescents born small for gestational age
Tierney, 2013 (816)	Carotid pulsatility index from Doppler	Subjects with Kawasaki disease have higher pulsatility index
Tryggestad, 2012 (695)	Small and large artery elasticity index	Obese youth had higher elasticity.
Urbina, 2009 (701)	Carotid ultrasound	Carotid stiffness higher in youth with obesity or T2DM compared to controls

Table 5.3 Published Pediatric PWV normal values*

Author, Year	Method†	Age (yrs) Mean ± SD	Number	PWV (m/sec) Mean ± SD
Ahimastos, 2003 (636)	C-F, F-D, tonometry	12.9 ± 0.2	N = 58 pre-, N= 55 post-pubertal	4.1 to 8.2
Avolio, 1983 (719)	Doppler ultrasound	Chinese subjects 3 - 20	108	6.2 to 10.2
Avolio, 1985 (97)	Doppler ultrasound	Chinese subjects 0.2 - 20	125	4.4 to 7.9
Collins, 2008 (817)	B-A, volume plethysmography	15.8 ± 2.4 15.9 ± 2.5	Male = 99 Female = 106	10.9 ± 1.4 10.4 ± 1.3
Collins, 2009 (697)	B-A, volume plethysmography	12 – 17	83 Americans age 12-14 15-17 390 Japanese age 12-14 15-17	 Male = 10.48 ± 1.26 Female = 10.23 ± 10.7 Male = 11.15 ± 1.37 Female = 10.35 ± 1.47 Male = 9.47 ± 1.17 Female = 9.32 ± 1.18 Male = 10.41 ± 1.07 Female = 9.52 ± 1.03
Fischer, (818)	C-F, oscillometric	5-19.6	Male = 156 age 5-8.3 8.4-10.8 10.9-14.1 14.2-19.6 Female = 158 age	*Also table by sex, age, height* 4.1 (3.4-5.0) 4.4 (3.6-5.1) 4.7 (3.8-5.7) 5.3 (4.2-6.2) 4.1 (3.4-5.4) 4.2 (3.4-5.4)

			5-8.3 8.4-10.8 10.9-14.1 14.2-19.6	4.5 (3.4-5.9) 4.8 (3.4-5.8)
Ge, 2007 (819)	C-Ft, C-R, tonometery	11.9 - 30	White male = 214 White female = 199 Black male = 129 Black female = 160	7.15 ± 0.91 7.03 ± 0.84 7.10 ± 0.83 7.20 ± 0.81
Hidvegi, 2012 (820)	'Aortic' (sternal notch to pubic bone)	3-18	Boys = 1802 Girls = 1572	5.5 ± 0.3 to 6.5 ±0.3 5.6 ± 0.3 to 6.4 ± 03, see tables for normal by age
Im, 2007 (750)	B-A, volume plethysmography	14.5 ± 1.2 14.8 ± 1.5	Male = 178 Female = 84	10.3 ± 0.9 9.6 ± 1.7
Jo, 2010 (821)	AA-AD, Doppler	1 month-15.8 yrs (mean 6.8 ± 4.7)	206	3.07 (2.99-3.15)
Kis, 2008 (752)	C-F, tonometry	6 - 23	133	5.02 ± 0.89
Kotsis, 2011 (755)	C-F, tonometry	21 ± 1	115	8.1 ± 2
Koudsi, 2007 (700)	SSN-Ao, infra-red and ultrasound probes	Neonates 1-3 days old	148	Maternal SBP < 108 mmHg = 4.77 ± 0.55; ≥ 108 mmHg = 4.41 ± 0.59
Kracht, 2011 (696)	C-F, oscillometric	11.1 ± 2.9	156	4.3 ± 0.6
Lurbe, 2012(659)	C-F, tonometry	8 - 18	424	4.96 ± 1.1

Miyai, 2009 (763)	B-A, volume plethysmography	15 – 17	754 subjects age 15 16 17	 Male = 9.79 ± 1.21 Female = 9.34 ± 0.97 Male = 10.02 ± 1.05 Female = 9.71 ± 0.96 Male = 10.52 ± 1.02 Female = 9.80 ± 0.94
Niboshi, 2006 (710)	B-A, volume plethysmography	Japanese children 14.8 ± 2.5 14.5 ± 2.6	 Male = 500 Female = 470	 9.97 ± 1.3 9.47 ± 1.2
Reusz, 2010 (822)	C-F, tonometery	6.5 – 19.9	1008 subjects age 6.55 – 9.91 9.92 – 13.27 13.28 – 16.63 16.64 – 19.9	*Also table of PWV by age, ht, sex* Male = 4.396 (3.106-5.902) Female = 4.496 (2.809-5.801) Male = 4.740 (3.275-6.391) Female = 4.779 (3.552-6.826) Male = 5.243 (3.640-8.021) Female = 5.113 (3.955-6.983) Male = 5.538 (3.725-7.999) Female = 5.335 (3.181-7.634)
Sarkola, 2012 (823)	C-F, C-R, F-Ft, tonometry	5-18 years	N = 97 subjects 5 – 9 10-14 15-18	 C-F 4.4 ± 0.9 C-R 6.6 ± 1.3 C-F 4.5 ± 1.0 C-R 6.3 ± 1.1 F-Ft 7.1 ± 1.5 C-F 5.5 ± 0.8 C-R 6.4 ± 0.8 F-Ft 6.7 ± 1.3
Urbina, 2010 (661;681)	C-F, C-R, F-Ft, tonometry	10 - 23 years	241 lean, non diabetic	C-F = 5.4 ± 0.7 C-R = 7.4 ± 1.1

				F-Ft = 8.0 ± 1.2
Urbina, 2012 (664)	C-F, tonometry	15 – 28	232 lean, non-insulin resistant	5.85 ± 0.85
Voges, 2012 (824)	MRI, thoracic aorta	16.4 ± 7.6	71	3.6 ± 0.7
Zhu, 2007 (637)	C-Ft, C-R, tonometry	17.6 ± 3.3	Normotensive White = 474 Black = 353	 C-Ft = 7.0 ± 0.1 C-R = 6.2 ± 0.1 C-Ft = 7.2 ± 0.1 C-R = 6.7 ± 0.1

*Only considered publications with sample size above 100 for healthy subjects, where raw PWV value was supplied.
†AA-AD = ascending aorta -proximal descending aorta AD-I = proximal descending aorta-abdominal aorta proximal to iliac bifurcation, B-A = brachial ankle, B-R = brachial radial , C-F = carotid-femoral, C-Ft = carotid-foot, C-R = carotid-radial, F-A = femoral-ankle, F-D = femoral-dorsalis pedis, F-Ft = femoral-foot, H-F = heart-femoral, H-I = heart-iliac bifurcation, H-L = heart-leg, SSN-Ao = supra sternal notch-abdominal aorta

Table 5.4.Normal values for AIx in adolescents and young adults.

Author, Year	Method	Age (yrs) Mean ± SD	Number	AIx (%) Mean ± SD
Lurbe, 2012 (659)	Radial artery tonometry	12.2 ± 2.2	424	1.31 ± 15.4
McEniery, 2005 (204;825)	Radial artery tonometry	18-20	Males = 172 Females = 133	-2 ± 8 5 ± 10
Urbina, 2010 (661)	Radial artery tonometry	17.8 ± 3.5	241	-0.52 ± 10.8
Urbina, 2012 (664)	Radial artery tonometry	20.8 ± 2.6	232	-0.48 ± 11.31

SECTION 6: Validation of Arterial Stiffness Devices

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When facing the question of validation of devices and methods, some questions need to be addressed:

1. Is there a “gold standard“ of measuring pulse wave velocity?
2. Are there studies comparing different methods and devices? How should the results be reported?
3. Are there any studies showing the clinical value of different methods and devices?
4. Special considerations

6.1 What is the “gold standard“ of measuring aortic pulse wave velocity?

- Invasive aortic PWV?
- Magnetic resonance imaging based PWV?
- Simultaneous acquisition of pressure (distension, flow) waves at carotid and femoral artery
- Dedicated carotid-femoral PWV devices?
- Is there a gold-standard of measuring travel distance non-invasively?

6.1.i Invasive aortic PWV:

This measurement has the advantage of being a simple, straightforward technique (measuring transit time (TT) simultaneously or ECG triggered and travel distance (TD) from catheter length). Of note, pressure waves measured at different points in the aorta travel only in one 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 (185;232;365;826-829). So far, one study investigated its relationship to clinical outcomes (232).

6.1.ii Magnetic resonance imaging based aortic PWV:

With this technique, TD can be measured very accurately due to many precise 3 dimensional imaging approaches. TT can be estimated, using dedicated sequences to derive flow signals. Flow signals as measured travel along the aorta in only one direction along a single path, yielding a physiologically correct measurement. However, the temporal resolution for TT assessment is relatively low in comparison to the other techniques, although this has been improved recently (830). The reproducibility and the accuracy with respect to invasive measurements may also depend on the methods used to determine TT (831;832), 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 with cardiovascular endpoints.

6.1.iii Simultaneous acquisition of pressure waves at the carotid and femoral artery:

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 have no or only minor effects on measured TTs (135), as long as a regular rhythm is present. In the presence of arrhythmias, measurements may be unreliable due to different intervals from ECG´s R-wave to the foot of the travelling wave.

6.1.iv Can dedicated devices for the measurement of cfPWV be recommended as non-invasive gold-standard?

Clearly, 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, which have been used widely in prospective trials showing an independent prognostic value of cfPWV (Complior device, ALAM medical; SphygmoCor device, AtCor medical).

6.1.v. Standardization of methods for comparison of devices

Because of the expansion of the field for non-invasive 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 (833). There are tables for sample size (90 subjects selected with a minimum of 83 for data analysis), age range (at last 25 in age range <30, 30-60, >60 years) and exclusion criteria (eg absence of sinus rhythm, significant arterial stenosis). There is also a specific description of the order of measurements between the devices so as to avoid the possibility systematic errors. A classification is also provided based on the variability of mean difference (MD) and standard deviation (SD) in relation to a reference device.

This protocol was recently used for the first time to validate a cuff based device (SphygmoCor XCEL ®) for detection of carotid femoral pulse transit time, with the aim to provide similar cfPWV values as those obtained with a femoral tonometer (SphygmoCor) (128). When the cuff measurement of pulse transit time 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 MD of 0.02 m/s and SD of 0.61 m/s.

6.1.vi The problem of non-invasive estimation of travel distance 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 (834). 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 (355). 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 (355), 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 being not a simple unidirectional path length (835), thereby rendering all determinations of the “real“ travelled path length somewhat elusive. Even sophisticated MRI-based measurements are valid only based 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, PWVs in the carotid artery can be 2-3 m/sec higher than in the aortic arch (836), and in humans the differences between aortic and carotid stiffness are higher in patients with hypertension and diabetes (837). Whether these differences can affect the actual cfPWV by 2%, or up to 10%, has been recently discussed (838). However, some standardization is obviously necessary, and comparisons with invasive PWV and MRI-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/sec) between invasive aoPWV and non-invasive cfPWW(185), whereas the direct distance method overestimated aoPWV by 2.9 m/sec. When the same TT (carotid-femoral TT derived from tonometry) was used, and TD was measured with MRI (aortic arch to femoral recording site minus carotid length from origin to recording site; again assuming equal velocities in carotid artery and aortic arch), the surface measurement closest to MRI TD estimate was carotid-femoral minus SSN-carotid (355). In another study, using MRI 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 (839). In all 3 studies, the direct carotid-femoral measurement led to a substantial overestimation of aoPWV. Although conversion factors between the different cfPWV values obtained with different methods to assess TD are available from collaborative projects (840), this panel recommends to use either the "subtraction method" (suprasternal notch – femoral recording site minus suprasternal notch – carotid recording site) or the "80 % method" (80% of the measured direct distance between carotid and femoral recording site) to estimate TD for cfPWV.

6.2. Comparison between different methods and devices, accuracy, repeatability, reproducibility

There are several studies published comparing different methods to measure PWV (Table 6.1).

When invasive and MRI measurements of aoPWV were compared, mean differences from as low as 0.2 (831) and 0.3 (167) m/sec to as high as 1.87 m/sec (829) have been reported, as well as correlation coefficients from 0.26 [9] to 0.71 (831).

When invasive aoPWV and non-invasive (tonometer- or mechanotransducer-based) cfPWV or baPWV was compared, differences could be attributed to 1) measurements at different time points, 2) measurements of different arterial segments, and 3) different methods of non-invasive

TD estimation (185). Mean differences ranged from 0.2 to 2.9 m/sec (185), and correlation coefficients typically were in the range of 0.7 – 0.87 (144;185;829).

When MRI-based aortic PWV and tonometer- or mechanotransducer-based cfPWV was compared, differences could be attributed to 1) measurements at different time points, 2) measurements of different arterial segments, and 3) different methods of non-invasive TD estimation. Mean differences ranged from 0.12 (841) to 1.7 m/sec (830), when cfPWV was compared with MRI-based PWV of the entire aorta, and from 2.46 (842) to 3.1 m/sec (424), when MRI-based aortic arch PWV was compared to cfPWV. Correlation coefficients ranged of 0.43 (841) to 0.83 (842).

The results of validation studies should be presented using the method of Bland and Altman (130), where the difference between the values obtained with the two devices is plotted against the mean value of both devices. The plot then shows the mean difference between the two methods / devices and the +/- 2 standard deviation – boundaries. Excellent, acceptable, and poor accuracy may be defined as in Table 6.2 (833). 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, as different estimations between the devices will result in systematic over- or underestimation of cfPWV.

The same criteria may be applied to intra- and interobserver repeatability / variability as well as reproducibility (two measurements separated by at least 24 hours).

6.3. Clinical validation: Which devices and techniques have been used in the clinical endpoint-studies?

Evidence today clearly shows that measurement of cfPWV is a potent and independent marker of cardiovascular risk and mortality. Data from > 25 clinical studies provide significant support for this statement. In this sense, measurement of cfPWV per se has been validated for risk stratification (Table 6.3).

We also have > 10 studies (although most of them with small sample size and few outcome events) reporting an association between baPWV and CV outcomes, with 2 negative studies. One limitation is that all studies have been performed in Japanese patients. Furthermore, TD for baPWV can obviously only be estimated, as there is of course no direct unidirectional propagation of pressure or flow from brachial to ankle. The formula used in the systems is based

on anthropometric data from Japanese individuals. In this sense, baPWV has been incompletely validated, particularly outside Japan, to predict CV outcomes.

6.4. How to deal with

- devices providing estimates of aortic PWV, using one-point measurements (Arteriograph, Mobil-O-Graph)
- local arterial stiffness (search terms: “local arterial stiffness“ “wall tracking“ “echo tracking“ “carotid stiffness“, “arterial distensibility“ “carotid distensibility“ “elastic modulus“

6.4.i Systems providing estimated aoPWV from waveform analysis:

There is some interest in techniques estimating aortic PWV from waveforms analysis, which would simplify the procedure. One device, the Arteriograph (Tensiomed), has been validated invasively (843): mean difference between invasive measurement and non-invasive estimate 0.05 m/sec, R=0.91) and non-invasively (844), although the working principle has been questioned on the basis of computer models (845). Furthermore, outcome studies with this particular device are pending. Another device, the Mobilograph (I.E.M., Germany), estimates aoPWV from wave separation analysis, age and blood pressure. A recent study (146) found acceptable agreement with tonometry (SphygmoCor, Australia) (mean difference 0.3 m/sec, SD 1.1 m/sec). One small study in patients with chronic kidney disease NKF stage 2-4 has already shown the independent prognostic value of estimated aoPWV (measured with the Mobil-O-Graph device) with respect to mortality (846). Although these devices hold a great potential for simplifying the measurement of PWV and, thus, enabling its use in clinical routine, currently due to the lack of evidence, no recommendations can be given.

6.4.ii Local (Carotid) arterial stiffness

Measurements of local arterial (carotid) stiffness relate changes in diameter to changes in local pressure. Diameters and their changes throughout the cardiac cycle can be measured, using B-mode ultrasound and video-image analysis, where precision is limited by pixel size (roughly 150 µm) (135). Nowadays, Echo-tracking devices are preferred, which allow a 6-10 times higher

precision (158). In addition, local pressures (instead of brachial pressures) are necessary for calculations of the various parameters of carotid artery and wall stiffness. A list of invasive validation studies for central pressures has been published recently (847). As far as carotid stiffness is concerned, no invasive validation studies are available so far. Table 6.4a shows comparative studies between different devices. They reveal that echo-tracking devices are more precise than B-mode based techniques, and that measures cannot be easily compared, when obtained with different techniques.

With respect to outcomes, in 8 out of 11 studies listed in Table 6.4, one or more of the arterial parameters listed had no relationship with outcome.

Table 6.1: Comparative studies using different techniques to measure PWV

Author	***n***	***Method 1***	***Method 2***	***Mean difference (1 minus 2) / 2 SD m/sec***	***Correlation coefficient***
Dogui (848)	46	MRI aortic arch PWV	Applanation tonometry cfPWV. TD: SSN-fem minus SSN-car	- 2.73 / n.a.	0.69
Joly (841)	32	MRI PWV (aortic arch-mid-descending aorta)	1. Applanation tonometry (Pulse Pen) 2. Mechanotransducers (Complior) cfPWV each. TD: SN-fem minus SN-car	1. – 1.01 / 4.13 2. 0.12 / 3.8	1. 0.47 2. 0.43
Salvi (849)	50	2 tonometers	1. Applanation tonometry (Pulse Pen) 2. Mechanotransducers (Complior) cfPWV each.	1. -0.15 / 0.62 2. 2.09 / 2.68	1. 0.99 2. 0.83
Rogers (850)	24	MRI PWV (aortic arch – abdominal aorta)	Tonometry (Millar SP 301) carotid-fem TD: manubrium-fem minus manubrium-car	0.3 / n.a.	n.a.
Dogui (842)	50	MRI aortic arch PWV (4 methods for TT estimation)	Applanation tonometry cfPWV (Pulse Pen device); TD: SSN-femoral minus carotid-SSN	-2.48 / -2.86 / -2.46 / -2.46 // SDs n.a.	0.70 / 0.69 / 0.34 / 0.59
Grotenhuis (167)	18	Invasive aoPWV (total/proximal/distal aorta)	MRI aoPWV (total/proximal/distal aorta)	-0.4 / -0.3 / -0.8// 2 S.D.s 2.0 / 2.0 / 1.6	0.53 / 0.69 / 0.71
Westenberg (831)	17	Invasive PWV (ao arch)	MRI PWV ao arch 1. in plane VE 2. through plane	1. 0.2 / 3.2 2. 1.3 / 3.4	1. 0.69 2. 0.26
Hickson (830)	157	MRI PWV (entire aorta)	1. Cf PWV tonometry (SphygmoC	1. 1.7 / 3.2 2. 1.4 / 3.4	3. 0.71 4. 2. 0.64

			or) TD: n.a. 2. Cf Cuff (Vicorder) TD:n.a.		
Redheuil (424)	111	MRI PWV (aortic arch)	Tonometry Cf PWV TD: SSN-fem minus SSN-car	-2.7, -2.8, -3.2, -2.3, -3.1, -2.7 in 3rd,4th,5th,6th,7th, 8th decade	0.71
Salvi (138)	68	2 tonometers (simultaneous measurement). TD: SSN-fem minus SSN-car	Consecutive ECG triggered applanation tonometry (Pulse Pen). TD: SSN-fem minus SSN-car	-0.17 / 1.2	0.98
Hickson (851)	122	Consecutive ECG triggered tonometry (SphygmoCor). TD: SSN-fem minus SSN-car	Simultaneous cuffs around neck and upper thigh (Vicorder). TD: SSN – top of thigh cuff	0.31 / 3.08	0.85
Weber (185)	135	Invasive aoPWV (ao arch-bifurcation)	Consecutive ECG triggered applanation tonometry (SphygmoCor). TD: 1. SSN-fem minus SSN-car 2. direct distance	1. -0.2 / 3.1 2. -2.9 / 3.4	1. 0.76 2. 0.73
Podolec (829)	107	Invasive aoPWV (aortic bulb-bifurcation)	Mechanotransducers (Complior). TD.:direct distance	- 1.87	0.70
Yamashina (144)	41	Invasive aoPWV (ascending aorta – 50 cm distal)	baPWV (PWV/ABI Colin Co.)	n.a.	0.87

Table 6.2: Accuracy criteria

Excellent: mean difference $\leq$ 0.5 m/sec and SD $\leq$ 0.8 m/sec
Acceptable: mean difference < 1 m/sec and SD $\leq$ 1.5 m/sec
Poor: mean difference $\geq$ 1 m/sec or SD > 1.5 m/sec

Table 6.3 Predictive value of carotid-femoral as well as brachial-ankle pulse wave velocity in clinical studies with cardiovascular events as outcomes measures.

First author	Journal	Publication year	Population	n	Primary outcome / significance	Method used for cfPWV measurement	Method used for travel distance assessment
Carotid-femoral PWV							
Verbeke (441)	Hypertension	2011	Renal transplant recipients	512	CV events	Tonometry / (SphygmoCor)	80 % direct distance cf
Laurent (133)	Hypertension	2001	Essential hypertensives	1980	All cause mortality	Pressure sensitive transducer (Complior)	Direct cf distance
Blacher (852)	J Hum Hypertens	2011	Geriatric men	331	All cause mortality		
Maldonado (853)	J Hypertens	2011	Population based	2200	CV events	Pressure transducer / Complior	Direct cf distance
Blacher (231)	Circulation	1999	Dialysis patients	241	All cause mortality	Doppler flow (aortic arch / carotid artery-femoral artery)	Direct cf distance
Boutouyrie (132)	Hypertension	2002	Essential hypertensives	1045	Coronary events	Pressure sensitive transducer (Complior)	Direct cf distance
Terai (235)	Hypertens Res	2008	Essential hypertensives	676	Stroke, CV events	Pressure transducer (FCP-4731)	Direct cf distance minus sternal notch-carotid
Cruickshank (155)	Circulation	2002	Typ 2 diabetics and glucose	470	All cause mortality	CW Doppler aortic arch / abdominal	Sternoclavicular notch – distal probe

			tested population sample			aorta	
Shoji (854)	J Am Soc Nephrol	2001	Dialysis patients	265	CV mortality	PWV meter (PWV-200)	1.3 x second intercostal space to femoral artery
Guerin (213)	Circulation	2001	Dialysis patients	150	All cause mortality	Doppler flow carotid artery – femoral artery	Direct cf distance minus carotid suprasternal notch
Inoue (855)	Circulation Journal	2009	Men undergoing medical check-up	3960	All cause and CV mortality	PWV meter	1.3 x second intercostal space to femoral artery
Laurent (187)	Stroke	2003	hypertensives	1715	Fatal stroke	Pressure sensitive transducer (Complior)	Direct distance
Mattace Raso (188)	Circulation	2006	population	2835	CV disease	Pressure sensitive transduce (Complior)	Direct cf distance
Meaume (186)	ATVB	2001	Subjects > 70 years	141	CV mortality	Pressure sensitive transducer (Complior)	Direct cf distance
Pannier (233)	Hypertension	2005	End stage renal disease	305	CV mortality	Pressure sensitive transducer (Complior)	Direct cf distance
Verbeke (856)	Clin J Am Soc Nephrol	2011	Dialysis patients	1084	CV events	Applanation tonometry (SphygmoCor)	Sternal notch-femoral minus sternal notch-carotid
Szeto (857)	Am J Nephrol	2012	Peritoneal dialysis patients	155	All cause mortality	Pressure sensitive transducer (Complior)	Direct cf distance

Shokawa (237)	Circulation Journal	2005	population	492	All cause and CV mortality	Transcutaneous pressure sensors (MCG400)	Direct cf distance
Verwoert (858)	J Human Hypertens	2012	Elderly individuals	2849	CHD events	Pressure sensitive transducer (Complior)	Direct cf distance
Mitchell (139)	Circulation	2010	General population	2232	CV events	Carotid and femoral tonometry	Suprasternal notch-femoral minus suprasternal notch-carotid
Sutton-Tyrell (157)	Circulation	2005	Older adults	2488	CV events	Doppler flow right carotid – right femoral artery	Direct cf distance
Protogerou (440)	Hypertens Res	2011	Very old individuals	259	All cause mortality		
Willum Hansen (189)	Circulation	2006	General population	1678	CV events	Piezoelectrical pressure transducers (Hellige GmbH)	Direct cf distance
Anderson (859)	Hypertension	2009	General population	174	Total mortality	CW Doppler aortic arch / abdominal aorta	Sternoclavicular notch – distal probe
Wang (156)	Hypertension	2010	General population	1272	All cause and CV mortality	Doppler flow carotid artery – femoral artery	n.a.
Zoungas (236)	Am J Kidney Dis	2007	Chronic kidney disease stages 4-5	207	CV events	Pressure transducer (Millar SPT – 301)	Sternal notch-femoral minus sternal

							notch-carotid artery
Ilyas (860)	QJM	2009	Suspected CAD	284	CV hospitalization + mortality	Applanation tonometry (SphygmoCor)	n.a.
Brachial-ankle PWV							
Ninomiya (861)	J Hypertens	2013	General population	2916	CV events	PWV/ABI (Omron)	Distance calculated from height
Kato (150)	Ther Apher Dial	2012	Hemodialysis patients	135	All cause mortality CV mortality	CAVI VaSera VS 1000	Distance calculated from height
Munakata (862)	Hypertens Res	2012	Essential hypertension	662	CV events	PWV/ABI (Colin Co.)	Distance calculated from height
Yoshida * (863)	Diabetes Care	2012	Typ 2 diabetes	783	CV events	Automated waveform analyzer	
Tanaka * (863)	Atherosclerosis	2011	Hemodialysis patients	445	CV events	PWV/ABI (Colin Co.)	Distance calculated from height
Amemiya * (864)	J Atheroscler Thromb	2011	Hemodialysis patients	186	All cause mortality	PWV/ABI (Omron)	Distance calculated from height
Nakamura (865)	Hypertens Res	2010	Typ 2 diabetes with CAD	564	CV events	PWV/ABI (Colin Co.)	Distance calculated from height
Turin (143)	Hypertens Res	2010	General population	2642	All-cause mortality	PWV/ABI (Omron)	Distance calculated from height
Miyano (866)	Hypertens Res	2010	Community-dwelling older adults	530	All-cause mortality, CV mortality	PWV/ABI (Colin Co.)	Distance calculated from height
Meguro (867)	Circ J	2009	Patients with heart failure	72	HF readmission + death	PWV/ABI (Colin Co.)	Distance calculated from height
Morimoto (868)	Am J Nephrol	2009	Hemodialysis patients	199	CV mortality	PWV/ABI (Omron)	Distance calculated from height
Matsuoka (142)	Biomed Pharmacother	2005	Elderly community-	298	CV mortality	PWV/ABI (Colin Co.)	Distance calculated from height

			dwelling people				
Kitahara (869)	Am J Kidney Dis	2005	Hemodialysis patients	785	All cause mortality	PWV/ABI (Colin Co.)	Distance calculated from height
Tomiyama (169)	Circ J	2005	Patients with acute coronary syndromes	215	CV events	PWV/ABI (Colin Co.)	Distance calculated from height

* negative study

Table 3: Outcome studies with cfPWV and baPWV. Search terms were: „aortic stiffness“, „pulse wave velocity“, „arterial stiffness“, „outcomes“, „mortality“, „cardiovascular events“, „myocardial infarction“, „stroke“, „heart failure“

Table 6.4a and 6.4b: Comparative studies (6.4a) and outcome studies (6.4b) using local arterial stiffness measurements with ultrasound.

Table 6.4a Comparison studies for local arterial stiffness devices

Author	Artery investigated	n	Index measured	Device 1	Device 2	Results
Palombo (870)	Carotid	105	Carotid distension Beta-Index	Esaote QAS	Aloka E-track	Distension sign lower, Beta-Index significantly higher with Esaote
Bianchini (871)	Carotid	21	Diameter Distension	B-mode based device	Radiofrequency based echo-tracking	Good agreement, B-mode based device less precise

Table 6.4b Outcome studies for local arterial stiffness (Carotid stiffness)

Author	Population	n	measurement	Outcome
Van Dijk * (872)	Impaired glucose tolerance	140	Carotid artery compliance and distensibility / ultrasound	Mortality
Blacher (873)	Dialysis patients	79	Carotid incremental modulus of elasticity / echo tracking	All cause mortality
Briet (203)	Chronic kidney disease	180	Carotid circumferential wall stress / wall tracking, Esaote	Progression of CKD
Dijk * (874)	Manifest arterial disease	2183	Carotid distensibility, Beta –Index, distensibility coefficient, Petersens modulus, Youngs modulus / Wall tracking (Scanner 200, Pie medical)	CV events
Yang * (875)	General population	10407	Carotid artery : strain, compliance, distensibility, pressure-strain, Youngs elastic modulus / ultrasound	CAD events* Stroke

Haluska * (876)	Primary prevention patients	719	Common carotid artery distensibility coefficient	All cause mortality CV events + mortality
Barenbrock (877)	Patients after renal transplantation	68	Common carotid artery distensibility coefficient / multigate Doppler system	CV events
Leone * (878)	Elderly individuals ≥ 65 yrs	3337	Carotid distension, carotid distensibility index*, Youngs elastic modulus*, Beta stiffness index* / B-mode ultrasonography (Ultramark 9)	Coronary events
Mattace-Raso * (188)	General population	2835	Carotid distensibility coefficient / Duplex scanner (ATL Ultramark IV)	CV events
Blacher * (879)	Dialysis patients	110	Carotid artery: incremental elastic modulus, compliance*, distensibility* / ultrasound	All cause mortality
Störk *(880)	Elderly men ()	367	Carotid artery: distensibility*, Petersons modulus, Youngs modulus, Beta-Index / wall tracking (Pie medical)	CV mortality

* negative study

SECTION 7: Pitfalls and Limitations of Arterial Stiffness Measurements

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The assessment of arterial stiffness is associated with a number of confounding factors and other limitations. These factors require due consideration in order to minimise their impact and allow high quality data to be obtained.

Physiological confounders

Of the physiological variables affecting arterial stiffness, the most significant is the vessel distending pressure (mean pressure) (397;881-883). This is in contrast to pulse pressure, which 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. Therefore, when assessing arterial stiffness, it is necessary to consider that the measured value will depend on the mean pressure. This is particularly important when assessing arterial stiffness in hypertensive patients, or investigating the effect of anti-hypertensive agents. The relationship between heart rate and arterial stiffness is less well defined, with acute studies showing positive associations (36;884;885), no association (35;886) or even inverse associations (887) between increased heart rate and various measures of arterial stiffness, including pulse wave velocity. These disparate results reflect that at least some of the studies may have been confounded by concomitant changes in mean pressure. Nevertheless, a recent study (39) demonstrated that although heart rate exerts a minimal influence on pulse wave velocity in the lower range of mean pressure values, an increase in heart rate results in a modest but significant increase in pulse wave

velocity at higher mean pressure values. Since blood pressure and heart rate vary considerably both within and between individuals, this must be taken into consideration when undertaking measurements of arterial stiffness. A suitable environment should be provided which has a stable temperature and is quiet. Participants should refrain from alcohol, vasoactive medications, or bouts of vigorous exercise, ideally for 12 hours. In addition, large meals, caffeine-containing food and drinks and smoking should be suspended for at least 2-4 hours prior to the measurements. Participants should also be allowed to rest, in the supine position for at least 10-15 minutes to ensure haemodynamic stability. Menstruating women should be studied at a similar phase in their menstrual cycle.

Other confounders

Whenever tonometry or ultrasound systems are used for sequential recording of pressure or flow waves, using ECG gating, care has to be taken that cardiac rhythm is stable. In the presence of arrhythmias, measurements may be unreliable due to different intervals from ECG´s R-wave to the foot of the travelling wave.

Perhaps the most important non-physiological confounder of pulse wave velocity measurements is the method used to calculate the wave travel distance. Carotid-femoral PWV is calculated as the distance travelled by the pressure wave divided by the time delay between the arrival of the pulse wave at the carotid and femoral sites (wave transit time). For measurement techniques other than MRI, the travel distance is typically estimated from surface measurements between the recording sites. These measurements should be as accurate as possible, since small errors in distance measurement may translate into much larger errors in the calculated pulse wave velocity. A tape measure is usually used, although calipers minimise the impact of body contours

and, therefore, are recommended. Different approaches are used to calculate wave travel distance, although the most common methods are the direct distance between the carotid and femoral sites (direct method) and the distance between the suprasternal notch and carotid site subtracted from the distance between the suprasternal notch and the femoral site (subtracted method). Each method results in different values of pulse wave velocity (840), making it difficult to apply threshold values, as proposed by recent guidelines (888). Although conversion algorithms between the two methods have been developed (889), these are likely to introduce further error. Therefore, the method of distance calculation should be clearly stated. Further data are required to validate the use of threshold values for pulse wave velocity.

Limitations of arterial stiffness measurements

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 and 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 prior to undertaking study or clinical measurements. In addition, the equipment required for these measurements is often expensive and lacking in portability, limiting the use of some techniques for measuring arterial stiffness to specialist research settings. This is especially the case for MRI- and ultrasound-based approaches, although a number of portable ultrasound systems are now available. Finally, although convincing outcome data are now available for pulse wave velocity, a more general

limitation of assessing arterial stiffness is the lack of therapeutic agents available to target the large arteries and promote arterial 'de-stiffening'. Further research in his area is clearly required.

Table 7.1 Recommendations for minimising confounding of arterial stiffness measurements

Environmental Factors

- Quiet room
- Stable temperature (ideally temperature-controlled)

Participant Factors

- Refrain from alcohol and vasoactive medication (ideally for 12 hours)
- Refrain from vigorous exercise (ideally for 12 hours)
- Refrain from large meals, caffeine-containing food and beverages, and smoking (at least 2 hours but ideally 4 hours)
- All women who still have menstrual periods should be studied at a similar phase in the menstrual cycle
- Allow participant to rest in measurement position i.e. supine (at least 10 minutes but ideally 15 minutes)

Measurement Factors

- Allow an adequate period of training for observers (ideally high quality recordings obtained in a minimum of 20 individuals prior to undertaking study measurements)
- Measure distances using calipers and state method of distance calculation used
- Measurements should cover at least one respiratory cycle
- Do not allow participant to speak or sleep during the measurement
- Always take duplicate or triplicate readings

- If repeated/follow-up measurements are required, take at the same time of day (ideally with the same observer)

SECTION 8: Considerations in interpreting Arterial Stiffness data

Authors: Samer Najjar, Thomas Weber, Julio Chirinos

Over the past decade, interest in arterial stiffness has rapidly grown. Whereas previously arterial stiffness was only assessed in a select number of research laboratories, the expanding interest in the field, the development of commercial devices and the inclusion of PWV in the European guidelines for hypertension led to a significant increase in the number of researchers and clinicians evaluating arterial stiffness and to a dramatic increase in the number of publications reporting arterial stiffness data. It is therefore critical to evaluate the factors that influence the measurement and values of arterial stiffness, as a necessary step for the appropriate interpretation of the data and for performing valid cross-study comparisons.

Methodologic considerations

Although carotid-femoral pulse wave velocity is recognized as the gold-standard for the non-invasive assessment of arterial stiffness (135), often arterial stiffness is measured in alternative (or additional) vascular beds. For example, several noninvasive commercial devices assess brachial-ankle PWV. Compared to 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.

For a given vascular bed, the values of PWV may also differ based on the specific device that is used to measure PWV. For example, Millasseau et al (890) assessed PWV 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 vs. maximum slope method with the Complior system), such that the same waveforms analyzed by the 2 devices could result in differences in PWV values of 5-15%.

Another important source of variation is the methodology used for the measurement of the distance travelled by the pulse wave. For example, some labs measure the distance between the carotid and femoral sampling sites. Others have argued that because the pulse wave is travelling concurrently up the carotid artery and across the aortic arch, the distance from the suprasternal notch to the carotid sampling site should be subtracted from the distance between the suprasternal notch to the femoral sampling site. Within the same individuals, using different methodologies for estimating the distance travelled by the pulse wave can lead to differences in PWV values of 30% (891). Using MRI as the gold standard for measurement of the distance travelled by the pulse wave, Huybrechts et al (839) found that that these methods respectively overestimate and underestimate the distance measured. Furthermore, the best estimate was obtained from a formula that used 80% of the distance from the carotid sampling site to the femoral sampling site. A recent expert consensus document advised that this latter formula be adopted for use (835). Weber et al (185) found that non-invasive assessment of carotid-femoral PWV with the SphygmoCor device corresponded best with invasive assessment of PWV when the distance travelled was assessed by subtracting carotid-suprasternal notch distance from suprasternal notch-femoral distance.

In summary, there are several methodologic considerations that need to be taken into consideration when interpreting PWV data. Factors such as the specific bed examined, the type of device used, the methodology used to assess the time of travel, and the formula used to estimate the distance travelled all affect the values of PWV measured, and therefore should be carefully evaluated when attempting to perform cross-study comparisons.

Although this discussion has mostly focused on PWV, it is important to note that PWV is not the only index of arterial stiffness. Admittedly, the appeal of PWV is in part related to the ease with which it is measured non-invasively, and thus its widespread use. However, there are additional indices of arterial stiffness that are also well validated, that have differing determinants, and therefore yield additional insights into the properties of the local or regional arterial trees being assessed. These indices are only modestly correlated with PWV, because they assess facets of arterial stiffness that contribute to, but are not the sole determinants of, the speed of pulse wave

propagation across the arterial tree. This underscores the importance of not viewing the various indices of arterial stiffness as interchangeable.

Determinants of arterial stiffness

Numerous factors have been shown to affect arteriosclerosis (43), which integrates the structural and functional changes in the vasculature that underlie arterial stiffening. However, the dominant determinants of arterial stiffness are unequivocally age and blood pressure (209). The age-associated increase in arterial stiffness is ubiquitously observed, albeit with varying degrees across populations (97), and within cohorts (309), reflecting differences in nutrition, physical activity, genetic determinants, smoking, cholesterol, blood glucose, and other factors known to affect arterial stiffness. The relationship between arterial stiffness and blood pressure is more complex and is now assumed to be bi-directional, as an increase in distending pressure leads to an increase in arterial stiffness, and conversely, an increase in stiffness can lead to an increase in systolic blood pressure. The relationship between arterial stiffness and blood pressure (and to a lesser extent age) can be further confounded by medications, particularly antihypertensive drugs, which affect the values of both arterial stiffness and blood pressure.

Thus, interpretation of arterial stiffness data needs to take into account the clinical characteristics of the cohort or patient population studied, including age, prevalence of disease states (e.g. hypertension, diabetes, atherosclerosis), medications, lifestyle considerations (diet, physical activity), and perhaps genetic factors.

Normative values of arterial stiffness

As discussed elsewhere in this statement (Section 3), PWV has been shown to be a potent and independent predictor of adverse outcomes, including development of hypertension, cardiovascular events, renal insufficiency, cognitive decline and mortality. Thus, there is a growing recognition that measures of arterial stiffness may serve as important screening tools in clinical practice. The field of hypertension was the first to suggest bringing this test to the bedside, when it included PWV/stiffness in the 2007 ESH/ESC guidelines for the management of hypertension (892), where a fixed cut off of 12 m/sec was proposed, as indicative of subclinical organ damage. A recent expert consensus that advocated the use of the 0.8 x direct carotid-femoral distance for measurement of distance travel suggested that the cutoff be shifted to 10 m/s

(derived by multiplying 12 by 0.8 then rounding up) (835). Nonetheless, it is recognized that using fixed thresholds has several limitations, including the fact that it does not take into account the 2 dominants determinants of PWV (age and BP). Clearly, a PWV value of 12.1 m/s carries different prognostic information in an 80 year old person vs. a 25 year old. This prompted an interest in studies attempting to establish reference values for various populations (363;893). The European Network for Non-Invasive Investigation of Large Arteries assembled the Reference Values for Arterial Stiffness' Collaboration whose task was to generate reference and normative values for PWV. A large database was established that collected clinical and arterial stiffness data from 13 centers distributed across 8 European countries (840). The analysis focused on subjects who had a measurement of PWV, after excluding individuals with genetic causes of hypertension, secondary hypertension, overt cardiovascular disease, diabetes mellitus, therapy for hypertension, or therapy for dyslipidemia. The methodology for assessing transit time was first standardized by analyzing the collected waveforms using the intersecting tangent algorithm because of concern that the point of maximal upstroke tends to underestimate PWV (890). Next, the path length was also standardized, with adoption of the direct measurement of carotid sampling site to femoral sampling site, with the 0.8 scaling factor. The cohort included 11,092 individuals, who yielded reference values of PWV stratified by age groups (<30, 30-39, 40-49, 50-59, 60-69 and $\geq$70). In addition, from the subset of individuals who had optimal or normal blood pressure and no additional cardiovascular risk factors, normative values for PWV were also generated according to age groups (840). However, it should be emphasized that these normative and reference values are predominantly applicable to measurements performed using the aforementioned methodologies.

In conclusion, we strongly support the call to standardize the methodologies for measuring 1) the pulse transit time, and 2) the distance travelled by the pulse waveform, where we support the use of 80% of the distance from the carotid sampling site to the femoral sampling site (185;835). These are necessary steps to 1) improve the interpretability of the data, 2) allow cross-study comparisons, and 3) generate population-level reference and normative values for PWV, which would be the ideal method for identifying outliers, i.e. individuals believed to be at increased risk for organ damage from excessive arterial stiffening.

SECTION 9: Arterial Stiffness: Future Needs

Authors: Edward G. Lakatta, Ian B. Wilkinson, John R. Cockcroft

Background:

Progressive changes occur throughout life in the structure and function of central arteries in numerous species, and include diffuse intimal and medial thickening, and enhanced stiffening of central arteries (98). Viewing the reality of aging from the arterial wall begins with the realization that the lifetime risk for arterial diseases, e.g. atherosclerosis and hypertension, increases exponentially with advancing age (Fig. 9.1), and given the demographic imperative that the number of older persons has, and will continue to, dramatically increase, the incidence and prevalence of these diseases in Western society will be nearly unfathomable.

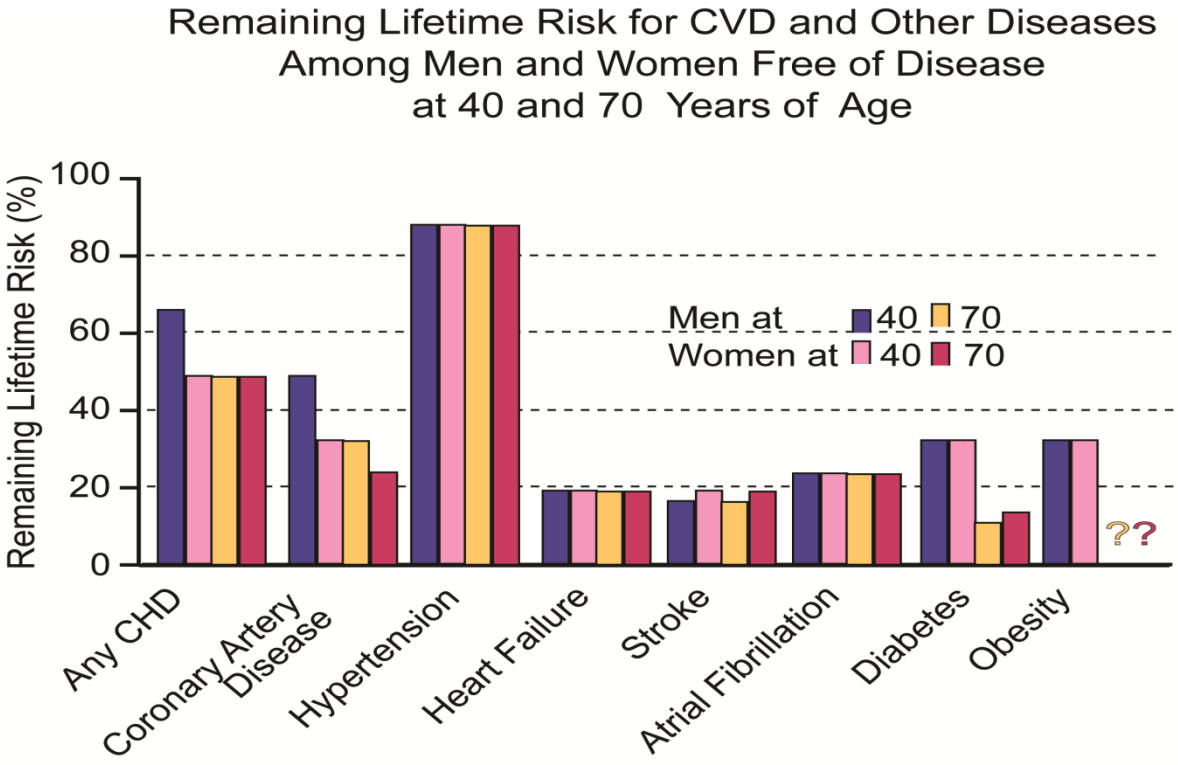

Figure 9.1 (Redrawn from Reference (894))

It is reasonable to hypothesize that specific mechanisms that underlie alterations in the arterial substrate that accompany “aging” may be intimately linked to the age-associated exponential increase in hypertension and atherosclerosis (100).

Stiffening of the central arteries beyond the age of 40 is a characteristic, but likely pathological, feature of advancing age (97;895). There are complex interactions among arterial stiffness, arterial pressure and age. Systolic pressure increases with age, and it has been argued that the age-associated increase in arterial stiffness is a major factor underlying the blood pressure increase and marked increase in predominantly systolic hypertension that accompany advancing age (98;896;897). Contrasting perspectives, however, argue that increasing stiffness with advancing age reflects not only specific age-associated changes within the arterial wall, but also results from chronic arterial wall distention in response to chronically increased arterial BP. Understanding how aging, stiffness and BP interact over time is a complex conundrum: Do age changes, per se, within the arterial wall drive the age-associated increase in arterial stiffness, or does the increase in arterial stiffness with advancing age the age-associated increase in predominately systolic BP, or is the age-related increases in arterial stiffening driven by the increase in BP that occurs with aging? Aortic stiffness can be non-invasively indexed as the carotid-femoral pulse wave velocity (135;840). Future blood pressure rise and hypertension, in fact, are predated by the initial measurement of PWV (305;309). A recent report from the Framingham study demonstrated that while increased aortic stiffness, as assessed by cfPWV was associated with an increased risk of incident hypertension, initial blood pressure was not, however, associated with risk of progressive stiffening (305). In addition a population based study demonstrated that in the Tsimanes, a tribe of forager-horticulturalists blood pressure did

not rise with age. Although PWV was not measured, pulse pressure, as a surrogate for aortic stiffening also rose little with age (898).

Beyond the BP-stiffness-age conundrum, results of epidemiologic perspectives that have delineated an independent risk of increased PWV for CV events, even when the impact of age, BP and other known risk factors are taken into account (133;139;157), suggest that prevention or reduction of aortic stiffening may carry substantial health benefits. However, the perquisite information required for such intervention studies is not presently available. An understanding of the "natural history" of PWV and BP, i.e. the rate at which PWV and BP increase with age, however, is required for the design of future clinical trials aiming to intervene on PWV. Further, knowing whether the rate of change is constant, varies by age or gender is required to perform correct power analyses and to determine the age/gender composition of an interventional study panel. Repeated, simultaneous measures of PWV and BP over time in a large number of individuals of a general population of a broad age range, therefore, are crucial to a genuine causal understanding of how BP and PWV and their relationship evolves over time, and to develop therapeutic strategies to reduce the risk of increasing arterial stiffening that accompanies advancing age.

Two potential interventions are currently available: BP-lowering drugs, which may act indirectly by reducing cyclical pressure load, and other interventions that act directly on the arterial wall to reduce stiffening. One additional problem with any trial that targets BP *per se* will be how to interpret the results. Given that PWV is dependent on distending pressure, any antihypertensive would be expected to reduce PWV passively because of a fall in mean (distending) pressure. Thus, to know whether a particular antihypertensive has a true direct effect on stiffness would require the use of an appropriate control antihypertensive that will lower pressure to the same

degree. Such trials are likely to be difficult because matching pressure between the two arms exactly is challenging and rarely achievable. Alternatively, as some suggest certain agents may have direct (BP independent) effects on the wall, and novel agents that target elements within the wall, which regulate stiffness such as matrix proteins or cross-links. Clearly the choice will depend on the availability of agents suitable to take into clinical trials but also knowledge of how BP and PWV track each other during aging over the entire age range – a lack of a clear relationship might make one wary of a simple trial which targets BP *per se*.

Specific future weapons required in the campaign to conquer arterial stiffening:

1) Measurement of PWV
    a. Simple cuff based devices that are operator independent will be crucial for PWV measurements to be widely introduced into routine clinical practice.
    b. Increased use of noninvasive techniques such as MRI which will allow assessment of regional aortic stiffness. This is because existing techniques for measuring aortic pulse wave velocity assume that the aorta is homogeneous. However recent data from MRI studies show this assumption to be false and different sections of the aorta stiffen differentially with age (830). Furthermore, different pathophysiological conditions may effect different aortic regions (e.g. calcification appears to favor the abdominal aorta) and indeed the same may have differential effects. This also applies when assessing the effect of drug therapy as using overall aortic PWV may miss real but subtle changes in regional stiffness.
    c. Currently non cuff based systems for assessing 24hr ABPM such as the ContiPress ® system are being piloted [http://cdn.medgadget.com/wp-content/uploads/2012/02/Poster-Medtech-Bazar-2012.pdf accessed April 21

2014]. Since this system records a brachial wave form it is possible that such systems may be adaptable in the future to assess both 24 hr central ABPM and also aoPWV

2) Longitudinal PWV measurements in a general population of a broad age range is required to design intervention studies with respect to power analyses and decisions regarding age and numbers of subjects to determine (a) the rate of change in PWV is over time and (b) whether the rate of change is constant over the entire age span.

3) As with #2 directly above, the rate of change of BP overtime, to establish the extent to which trajectories of BP and PWV track each other and how this relationship changes over a lifetime. This is required to inform whether BP-lowering drugs are sufficient at all ages.

4) Although a number of small studies have suggested that various lifestyle interventions may produce BP independent decreases in PWV, to date the best evidence available in terms of therapeutic intervention suggests that ACE inhibition may produce decreases in arterial stiffness beyond a blood pressure lowering effect (104;899). Much larger meta-analyses of individual patient data will be required in the future to be sure that decreases in PWV following therapy are truly, in part blood pressure independent.

5) Enhanced definition of events occurring at the vascular molecular/cell/matrix levels as arteries stiffen, in order to inform translation of these discoveries into the development and application of novel therapies.

Summary

In summary, ‘‘aging’’-associated arterial changes and those associated with hypertension (and early atherosclerosis and diabetes) are fundamentally intertwined at the cellular and molecular levels. In humans, other well-known risk factors (e.g., excess food intake, altered dietary lipid and metabolism, smoking, and lack of exercise) likely interact with this arterial substrate that has been altered during aging, and that renders the aging artery a “fertile soil” that facilitates the initiation and progression of these arterial diseases. Some lifestyle and pharmacologic 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 life style interventions may produce BP independent decreases in aoPWV, to date the best evidence available in terms of therapeutic intervention suggests that ACE inhibition may produce decreases in arterial stiffness beyond a blood pressure lowering effect (104;899). Much larger meta-analyses of individual patient data will be required in the future to be sure that decreases in PWV following therapy are truly, in part blood pressure independent. The cellular/molecular proinflammatory mechanisms driven by Ang II and other growth factors (Figure 1.3) 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.

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Abbreviations used in this Statement (unit of measure, when applicable)

ACE Angiotensin converting enzyme
AGE Advanced Glycation End-product
ARB Angiotensin Receptor Blocker
AIx Augmentation Index – a ratio expressing the relationship of forward and backward traveling waves in the central aorta (unit-less, or sometimes expressed as %)
Ang Angiotensin
BP Blood Pressure
baPWV Brachial-Ankle Pulse Wave Velocity (a measure of arterials stiffness; meters/second)
cfPWV Carotid-Femoral Pulse Wave Velocity (a standard measure of arterial stiffness; meters/second)
CFR Coronary artery Flow Reserve
CKD Chronic Kidney Disease
CV Cardiovascular
CVD Cardiovascular Disease
Δ Delta (i.e. change)
D Diameter (mm [often])
DM Diabetes Mellitus
DPTI Diastolic Pressure Time Index
eGFR Estimated Glomerular Filtration Rate (typically from the MDRD equation; mL/min/1.73m^2)
E Young's Elastic Modulus
E_p Peterson's Elastic Modulus
E_{inc} (incremental) Elastic Modulus (dynes/cm^2)
ECG Electrocardiogram
Ea Arterial Elastance (a measure that relates end systolic pressure to LV stroke volume)
ECM Extracellular Matrix
EECP Enhanced External Counter-Pulsation
eNOS Endothelial Nitric Oxide Synthase
ESC European Society of Cardiology
ESH European Society of Hypertension
ESRD End Stage Renal Disease
ET Endothelin
Ew Wasted left ventricular workload energy
fdPWV Femoral-Dorsalis Pedis Pulse Wave Velocity (a measure of arterials stiffness; meters/second)
GFR Glomerular Filtration Rate (a measure of kidney function; mL/minute)
GTF Generalized Transfer Function
GWAS Genome Wide Association Studies
h Wall Thickness (mm or μm)
HF Heart Failure
IDI Integrated Discrimination Improvement (statistics procedure)
K Bulk Elastic Modulus
LDL Low Density Lipoprotein
LOE Level of Evidence
LPK Lewis Polycystic Kidney (rodent model of arterial calcification)
LV Left Ventricle
LVH Left Ventricle Hypertrophy
LVOT Left Ventricle Outflow Tract
MAP Mean Arterial Pressure (mmHg)

MMP Matrix Metalloproteinase
MRI Magnetic Resonance Imaging
NIR Net Reclassification Index (ratio)
NPRA Natriuretic Peptide Receptor Type A
P Pressure (mmHg)
PC-MRI Phase Contrast Magnetic Resonance Imaging
PP Pulse Pressure (systolic minus diastolic pressure; mmHg)
PWA Pulse Wave Analysis – use of an arterial waveform to interrogate vascular function (units vary)
PWV Pulse Wave Velocity – the standard measure of arterial stiffness (meters/second)
Q Perfusion (mL/min) or Flow velocity (cm/second)
ρ Rho: Blood Density
RM Reflected wave Magnitude (mmHg)
SBP Systolic Blood Pressure
SD Standard Deviation
SPTI Systolic Pressure Time Index
SVR Systemic Vascular Resistance (dynes-second/cm^5)
T Tension
TD Travel Distance (millimeters or meters)
TG Transglutaminase (enzyme)
TT Transit Time (milliseconds, or seconds)
VENC Velocity-Encoding Sensitivity (an MRI technique to measure flow velocity)
VSMC Vascular Smooth Muscle Cell
Zc Characteristic aortic impedance (also called Zo; measures aortic pressure-flow relationship; ((mmHg*sec)/mL)

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