HHS Public Access

Author manuscript

Hypertension. Author manuscript; available in PMC 2015 September 29.

Published in final edited form as:

Hypertension. 2015 September ; 66(3): 698–722. doi:10.1161/HYP.0000000000000033.

Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness:

A Scientific Statement from the American Heart Association

Raymond R. Townsend, MD, FAHA [Chair], **Ian B. Wilkinson, MD, DM, FRCP, FAHA [Vice-Chair]**, **Ernesto L. Schiffrin, MD, PhD, FAHA [Vice-Chair]**, **Alberto P. Avolio, BE, PhD**, **Julio A. Chirinos, MD, PhD**, **John R. Cockcroft, FRCP, FESC**, **Kevin S. Heffernan, PhD**, **Edward G. Lakatta, MD**, **Carmel McEniery, PhD**, **Gary F. Mitchell, MD**, **Samer S. Najjar, MD**, **Wilmer W. Nichols, PhD**, **Elaine M. Urbina, MD, MS, FAHA**, and **Thomas Weber, MD, FESC on behalf of the American Heart Association Council on Hypertension**

Introduction

Much has been published in the last 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 regarding the nomenclature, methodologies, utility, limitations, and gaps in knowledge in this rapidly evolving field. The following represents an executive version of the much larger Online 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 both “PWV” and variations such as “cfPWV” are used. The use of “PWV” (for pulse wave velocity) without modification is used in the general sense of arterial stiffness. The addition of lowercase modifiers like ‘cf’ (for carotid femoral, as in cfPWV) is used when speaking of specific segments of the arterial circulation.

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

In the approximately three decades of clinical use of pulse wave velocity measures in humans we have learned much about the importance of this parameter. Pulse wave velocity has proven to have independent predictive utility when evaluated in conjunction with standard risk factors for death and cardiovascular disease. However, the field of arterial stiffness investigation, which has literally exploded over the last 20 years, has proliferated without logistical guidance for clinical and translational research investigators. This

Corresponding Author: Raymond R Townsend MD, University of Pennsylvania, Nephrology, 122 Founders Building, 3400 Spruce Street, Philadelphia, PA 19104 USA, Office phone: 215-662-4630, Office facsimile: 215-662-3459, townsend@exchange.upenn.edu.

Summary Statement, commissioned by the American Heart association Council for High Blood Pressure Research represents an effort to provide such guidance, drawing on the expertise of experienced clinical and basic science investigators in Europe, Australia and the USA. Recommendations made in this statement are assumed to refer to the research aspect of arterial stiffness investigations, unless accompanied by language that emphasis clinical usage as well, and are based on the grid in Table 1.

Section 1. What is arterial stiffness?

Recommendation

- **1.1** It is reasonable to measure arterial stiffness clinically by determining pulse wave velocity (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, since it affects the manner in which 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, where wall stiffness can be affected by endothelial function through modulation of smooth muscle tone or by altering the integrity of the extracellular matrix. As will be 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 usage and stiffness has been measured in most named large arteries in humans (17). Arterial stiffness is also estimated by measuring pressure and/or diameter in a vessel and applying one or several of the now extensive formulae to the data to derive a value that reflects this inherent property of all arteries (18).

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 on the basis of equations such as Moens-Korteweg, or Bramwell Hill with which these measures agree (18). 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, these 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, comparing the systolic pressure at the brachial artery with that at the proximal aorta, and sometimes reported as an augmentation index, are presented as “stiffness” parameters. Such measures are the result of several factors, including, but not limited to arterial stiffness (this is described further in the section on Wave Reflection) (19).

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. Due to the anatomical arrangement of the elastin and collagen fibers, elastin engages at low distension (hence at low pressure) and collagen at higher distension (and pressure) (20). 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, the 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 (16)). Active categories include endothelial function as it relates to nitric oxide and endothelin, as well as vascular smooth muscle where higher resting tone is associated with increase in arterial stiffness (21). Inflammation, oxidative stress, and turnover in the extracellular matrix of the vessel wall are additional active contributors to arterial stiffness (22). In addition, sympathetic tone and genetic polymorphisms appear to also 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, where a greater degree of functional effects would be manifest in more muscular arteries (e.g. carotid, iliac) compared to larger non-muscular conduit arteries (e.g. aorta) [callout i.ii here]

Section 2: Devices used to measure pulse wave velocity

Recommendations

- **2.1** You should non-invasively determine arterial stiffness by measuring carotid-femoral pulse wave velocity (Class I, Level of Evidence A) (2;3).
- **2.2** Pulse wave velocities measured in other vascular segments, such as ankle-brachial, or the determination of the cardiac-ankle vascular stiffness index, are useful in cardiovascular outcome predictions in Asian populations, but longitudinal studies in the US/Europe by these methods are lacking (Class I, Level of Evidence B) (4;5).
- **2.3** Single point estimates of pulse wave velocity are not recommended because there is a lack of evidence of cardiovascular outcome prediction in longitudinal studies. Measurement of pulse wave velocity in other arterial segments such as

carotid-radial is not recommended because it does not predict outcomes (Class III, Level of Evidence B) (6).

Measurements of pulse wave velocity (PWV) are undertaken using several methodologies, some of which require sophisticated equipment (MRI) and software (some ultrasound & MRI devices). These fall into four 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—A number of devices based on this technology are available and have been extensively used in published research. Tonometry-based techniques (e.g. SphygmoCor ® device, AtCor Medical, Australia) uses a piezoelectric Millar tonometer which is placed at any two sites where a pulse is detectable. There is only one tonometer attached to the unit so PWV measurements require two sequential 10–20 second readings, gated to the ECG, to be taken. The average transit time is then derived using the R wave of the ECG as a reference point, and PWV calculated based on the inputted distance measurement. The SphygmoCor device has been used in Anglo-Cardiff Collaborative Study of arterial stiffness (23) and the Chronic Renal Insufficiency Cohort (CRIC) study of chronic kidney disease (24), as well as other cohorts and intervention studies. Newer versions of this device use a cuff and tonometer system to record simultaneous pressure waves (25). Published reproducibility of the PWV with the SphygmoCor, as judged by Bland-Altman plot analysis, is good (26).

Mechano-transducer based techniques (e.g. Complior ®, ALAM Medical, France) uses similar principles, but allows simultaneous measurement between sites using distension sensors. The Complior software provides an on-line pulse wave recording and automatic calculation of the PWV (27). This device has been used extensively in epidemiologic studies in Europe and 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 (28).

Other tonometry-based devices (e.g. PulsePen ®, DiaTecne, Italy) use an ECG signal and a hand held tonometer (similar to the SphygmoCor) to perform carotid-femoral PWV 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 (29). The reproducibility of the PulsePen, as judged by Bland-Altman plot analysis, is good (30).

Still other tonometry-based devices (e.g. those used by Cardiovascular Engineering, Inc., Norwood, MA) use 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 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 (31) and Reykjavik Studies (32), as well as other cohorts and intervention trials. Reproducibility of the PWV by this method is, reportedly, good (Gary F. Mitchell, personal communication).

Devices using cuffs placed around the limbs or the neck that record pulse wave arrival oscillometrically—Oscillometric-based devices (e.g. VP1000 ®, Omron Healthcare, Japan) rely on four oscillometric cuffs – placed on both arms (brachial) and ankles to calculate 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). Newer models (e.g. VP2000) have additional probes that can be secured in place (with straps) that detect carotid (CAP) and femoral (FAP) pulses simultaneously (i.e. 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 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, mainly in Asia, and independently predicting loss of kidney function (33), cardiovascular disease (34), and all cause death (35). Published reproducibility of the PWV with the VP1000, as judged by Bland-Altman plot analysis, is good (36).

Cuff-based devices (e.g. Mobil-O-Graph ® (IEM, Stolberg, Germany) capture brachial blood pressure and brachial waveforms (causal and 24 hour), to estimate central aortic pressures, and to estimate carotid-femoral pulse wave velocity (37;38). The Mobil-O-Graph 24 h PWA ABPM device 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 approximately 10 seconds to record the pulse waves. Subsequently, central pressure curves are obtained using 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 (39). The Mobil-O-Graph aortic PWV values have been validated by direct intra-arterial measurement in the catheterization laboratory (40). Reproducibility of the Mobil-O-Graph, as judged by Bland-Altman plot analysis, is good (41).

Some cuff-based devices (e.g. Vasera ®, Fukuda Denshi, Japan) use cuffs on all four 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 (42). In addition to the cardio-ankle vascular index ('CAVI'; which is derived from the cardio-ankle PWV) it also provides an ankle-brachial index. This device has been used mainly in Japan for longitudinal studies of dialysis patients (4) as well as in community studies of cognitive decline (43). Reproducibility of the Vasera, as judged by Bland-Altman plot analysis, is good (44).

Ultrasound approaches—Ultrasound can be used to assess vessel distension and derived stiffness indices, or flow waveforms to calculate PWV. Distension waveforms can be assessed using ultrasound transducers at a variety of locations, but often the carotid and femoral sites are employed. 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 distension waveform, using dedicated software (e.g. ARTLAB ®, ESAOTE, Italy). With a value for the pulse pressure, the operator can determine distension and compliance. Often brachial artery pressure is used rather than local pulse pressure, which may introduce inaccuracies, as may any delay between distension and BP assessment. Pulse wave speed (c) and other indices of elasticity – such as incremental elastic modulus (Einc) - can also be derived as discussed earlier. It is worth noting that most ultrasound systems and software produce a time average waveform, and mathematically this will yield different values for stiffness indices compared to calculating distension beat-by-beat and then averaging.

In addition, ultrasound is 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 (45;46). The Online Supplement (Section 6) has more discussion of this aspect and device comparisons (Online Supplemental Table 6.4).

Doppler ultrasound may be used to record flow waveforms from accessible sites from which PWV can be estimated in a similar manner to PWV based on pressure waveforms. Waveforms may be recorded either sequentially with ECG gating, or simultaneously (47). Typically one 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 supra-sternal notch 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 (48). Identifying the foot of the flow wave can be more challenging than the foot of a pressure wave. However, such techniques have shown independent predictive value for cardiovascular outcomes, and death, in longitudinal studies of diabetics (48), the healthy elderly (49) and a general population (12). Published reproducibility of ultrasound-based PWV, as judged by Bland-Altman plot analyses, is good (50;51)

Magnetic resonance imaging (MRI)-based approaches—MRI can be applied in much the same way as ultrasound to determine distension-based indices 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 are offset against poorer time and spatial resolution and cost.

Phase contrast MRI (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) (52;53), 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 (54–57). More research is needed in regards to the optimal algorithm to measure the time delay between the foot of the flow waves using phase-contrast MRI.

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. Good reproducibility of PWV by phase-contrast MRI has been reported, with intra-class correlation coefficients ~0.90 (58).

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 Supplement provide greater detail about this.

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). Reproducibility

is generally good and most devices/approaches have been in use for at least a decade. Other approaches to measuring arterial stiffness are covered in the Online Supplement Section 2.

Section 3. Why is arterial stiffness important?

Recommendation

- **3.1** It is reasonable to measure arterial stiffness to provide incremental information beyond standard cardiovascular disease risk factors in the prediction of future cardiovascular disease events (Class IIa; Level of Evidence A) (3)

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 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 carotid-femoral PWV (cfPWV) is associated with increased risk for a first or recurrent major cardiovascular disease event (2;3). 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 (3;31). 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 (59;60). 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 (61). 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 (3).

Hypertension—The association between arterial stiffness and hypertension is well established (62–66). 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 found that higher arterial stiffness, as assessed by cfPWV, was associated with blood pressure progression and incident hypertension 7 years later (62). 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 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 (63–66).

High aortic stiffness is associated with increased blood pressure lability (67–69). A stiffened vasculature is less able to buffer short-term alterations in flow. Increased aortic stiffness is

also associated with impaired baroreceptor sensitivity (67;70–72). 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 (73).

Cardiac disease—Excessive arterial stiffness represents a compound insult on the heart. Aortic stiffening increases left ventricular systolic load, which contributes to ventricular remodeling and reduced mechanical efficiency. This leads to an increase in myocardial oxygen demand (74), compounded by a reduction in diastolic coronary perfusion as pulse pressure widens and diastolic blood pressure falls with aortic stiffening (75). Arterial stiffening may be associated with impaired measures of left ventricular diastolic function (76;77), which may increase cardiac filling pressure and further limits coronary perfusion. Finally, arterial stiffness is associated with atherosclerosis (78–81), which may further impair ventricular perfusion, possibly leading to catastrophic reductions in ventricular function during ischemia (75).

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 (77;82–86). 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 (87). Arterial stiffness is independently associated with an increased risk of heart failure (88) and is increased in patients with established heart failure whether left ventricular function is preserved or impaired (89–91).

Peripheral vascular function—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 (92). Arteriosclerosis also has important implications for 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 (32;93;94). Increased aortic stiffness and excessive pressure pulsatility are associated with increased resting microvascular resistance and markedly impaired post-ischemic reactive hyperemia in the forearm (95). 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 (96–99). Indeed, a recent study demonstrated a significant relationship between aortic PWV and media-lumen ratio of small resistance arteries in a cohort of hypertensive patients after adjustment for age and blood pressure (100). Dynamic tone in

small arteries is also affected by pressure pulsatility (101–104). 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.

Central Nervous System—High flow organs such as the brain and eye are particularly sensitive to excessive pressure and flow pulsatility (105). High local blood flow is associated with low microvascular impedance, which facilitates penetration of excessive pulsatile energy into the microvascular bed (32). 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, which may be ischemic or hemorrhagic (106;107). This may be mediated through atherosclerosis, with increased stiffness contributing both to atherogenesis and risk for plaque rupture (108), through atrial enlargement and fibrosis which can trigger atrial fibrillation, providing a cardiac source for embolus (87), or through diastolic flow reversal in the aorta, which could disrupt and redirect plaque from the distal arch into the carotid circulation (109). 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 (110).

Arterial stiffness is also associated with impaired cognitive function in selected (111–115) and community-based samples (32;116–120). 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 (121).

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 nearly to 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 (122;123). Recently increased renal pulsatility has been correlated with CV and renal outcomes (124). Numerous studies have demonstrated modest but robust associations between increased pulse pressure or PWV and reduced glomerular filtration rate (GFR) or proteinuria (125–131). 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 (132). 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 (133–135). 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 ESH/ESC guidelines for the management of hypertension (136), where a fixed cutoff of 12m/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) (137). 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 vs. a 25year-old person. Variability of cfPWV with age prompted an interest in attempting to establish reference values for various segments of the population (137;138). 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 cfPWV. The cohort included 11,092 individuals, who yielded reference values of cfPWV stratified by age groups (in years: <30, 30–39, 40–49, 50–59, 60–69 and >70). In addition, from the subset of individuals who had optimal or normal blood pressure and no additional cardiovascular risk factors, normative values for cfPWV were also generated according to age groups (139). However, it should be emphasized that these normative and reference values are predominantly applicable to measurements performed using the aforementioned methodologies.

Despite the attractiveness of age-relative normative thresholds, it is important to recognize an age-related increase in cfPWV should not necessarily be viewed as inevitable or indeed a normal part of the ageing process. Although cfPWV increases exponentially with aging in most populations, it appears to rise much less rapidly in truly rural or indigenous populations (140;141), as Trusswell reported for blood pressure in the 1970s (142). 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 as such, 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** We recommend that you quantify both time-resolved central pressure and central aortic flow 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** We recommend the use of pressure-flow analyses, which are considered the gold standard assessment, to determine left ventricular (LV) afterload (Class I, Level of Evidence A) (7;8).
- **4.3** Effective arterial elastance (Ea) should not be used as an index of pulsatile LV afterload or arterial stiffness, since it represents a poor index of pulsatile load and is not significantly influenced by arterial stiffness (Class III, Level of Evidence B) (9;10).
- **4.4** We recommend the use of wave separation analysis, as opposed to aortic augmentation index, when investigations are specifically focused on the role of wave reflection as either an exposure for a cardiovascular outcome or as a target for intervention (Class I, Level of Evidence B) (11–13).

The mechanical “afterload” imposed by the systemic circulation to the pumping left ventricle (LV) is the aortic input impedance, and is an important determinant of normal cardiovascular function as well as a key pathophysiologic factor in various cardiac and vascular disease states. In the presence of a normal aortic valve, LV afterload is largely determined by the elastic properties (arterial stiffness), arteriolar caliber and wave reflection characteristics of the arterial tree (“arterial load”) (8). Arterial load is complex, time-varying, and cannot be characterized by a single number or index. LV afterload is composed of a “steady” and a “pulsatile” component and can be described by the following indices: (1) Systemic vascular resistance (SVR); (2) Aortic characteristic impedance; (3) Total arterial compliance; (4) Wave reflection amplitude; (5) Reflected wave transit time.

SVR, the ***steady*** component of LV afterload, is largely determined 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) 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 (143;144), or estimated in the time domain from the aortic pulsatile pressure alone (18).

Furthermore, it should be recognized that: (1) afterload affects, in a reciprocal fashion, the pressure and flow waves generated by the LV; (2) pressure and flow waves are not only dependent on load, but are also strongly influenced by LV structure and function.

Flow can be measured invasively using a flow wire, or non-invasively with MRI or with pulsed wave Doppler echocardiography interrogating the LV outflow tract (LVOT). Central aortic pressure can be measured invasively with a pressure sensing catheter or wire, or via radial arterial tonometry and a general transfer function (GTF) which synthesizes a central aortic pressure waveform (18), or by carotid arterial tonometry. For non-invasive assessments, calibration of central pressure waveforms should be performed using peripheral diastolic and mean arterial pressures, which (in contrast to systolic pressure) remain relatively constant throughout the arterial tree (7). To obtain central aortic pressure

waveforms, calibration of the radial artery waveform should be performed using peripheral systolic and diastolic pressures (1;18).

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 (74;145). 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) (77;146–148). In health, there is an increase (or amplification) in the pulse pressure as the pulse wave travels from the proximal aorta to the periphery. Increasing aortic wave reflection amplitude increases aortic systolic pressure and decreases the gap between central and peripheral pulse pressure and dampens (or reduces) this amplification. Decreasing wave reflection amplitude with antihypertensive therapy and/or exercise conditioning increases the gap (and amplification) and reduces target organ damage (149). Conversely, a reduction in pulse pressure amplification is associated with overt target organ damage and independently predicts future cardiovascular mortality (150;151).

Thus, pulse pressure amplification has been proposed as a potential mechanical biomarker of cardiovascular risk and global arterial function. 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 (18;152).

Once measures of central aortic pressure and flow are obtained, these 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 wave forms 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 the Online Supplement (Figure 4.3). 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 (153–155). 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 (RM) is expressed as the ratio of the amplitudes of reflected/forward pressure waves (155), while reflection (or augmentation) index (AIx) is the ratio of the amplitude of the reflected wave and central aortic pulse pressure. These two variables (RM and AIx) are similar and are measures of wave reflection strength (or intensity). Reflected pressure waves arriving at the proximal aorta increase the late systolic load of the left ventricle, thus altering the loading sequence. Increased wave reflection amplitude and/or a left ventricular loading sequence characterized by late systolic load have been shown to cause myocardial hypertrophy (146;156;157), myocardial fibrosis (156), systolic and diastolic myocardial dysfunction (82;84;158–164) and to strongly predict

an increased risk of future heart failure (11;163). Increased wave reflections have also been shown to predict all-cause 15-year mortality (12).

Since invasive recordings of central aortic pressure and flow waves and pulse wave analysis can only be made in a select number of patients in the catheterization laboratory, techniques have been developed recently that enable the non-invasive determination of the above variables (165;166) in large cohorts with similar results (145;167–172)). 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 to obtain the non-invasive 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 while 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 (18;173–177). The first shoulder is an estimate of forward traveling wave amplitude while the second shoulder is an estimate of reflected wave amplitude. The characteristics of the reflected wave depends upon 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 (18;173–177).

Effective arterial elastance (Ea), computed as the ratio of end-systolic pressure to stroke volume, was proposed as a lumped parameter of resistive and pulsatile LV afterload (178) and is increasingly used due to the simplicity of its computation. However, Ea is almost entirely determined by the product of heart rate (a cardiac property) and SVR (179;180), and (despite its name) does not reflect or characterize pulsatile LV afterload (9;10). 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 blood pressure and LVH, 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 (167;181–183). In most countries, thiazide diuretics are the cheapest antihypertensive drugs available and they are the recommended first-line treatment for hypertension in the US (JNC 7) (184). Diuretics and pure β-blockers decrease blood pressure but have little, if any, direct

(active) effect on arterial properties and wave reflection characteristics. Selective and nonselective aldosterone blockers attenuate cfPWV and AIx (185;186) in select patient groups by increasing nitric oxide (NO) bioactivity and improving endothelial vasodilator dysfunction (187). Vasodilating drugs, 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 (188). 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 (189–191). ACE inhibitors, ARBs and CCBs are the most commonly used vasodilator drugs. These drugs appear to have little direct effect on stiffness of elastic arteries like the aorta independent of blood pressure reduction (18;183), although some studies question this (192–194). A recent meta-analysis observed that ACE inhibitor therapy improved the stiffening of arteries as reflected by PWV and reduced arterial wave reflections as assessed by augmentation index (AIx) when compared with placebo (195). Beta-blockers appear to show less benefit on central aortic pressure compared with ACE inhibition (e.g. in CAFÉ (196)), but less is known about newer beta-blockers that feature either concurrent alpha blockade (carvedilol) or nitric oxide stimulation (nebivolol).

Several non-pharmacological interventions reduce arterial stiffness and wave reflections, including aerobic exercise training (197;198), dietary changes (including weight loss and salt reduction) (199–202), passive vibration (203) and enhanced external counter-pulsation (EECP) treatment (204). For maximum cardiovascular benefits these interventions must be initially introduced acutely and continued over an extended period of time. While the effects of exercise on arterial stiffness and wave reflections have been studied for more than half a century (205), many aspects remain unclear. It appears that the effects depend on the type (aerobic or resistance), on the intensity, and on the duration of exercise [acute or chronic (endurance, training, conditioning)]. Multiple studies attest to the benefits of regular aerobic physical exercise in advanced age, hypertension, diabetes, coronary artery disease and heart failure and to the improvement in oxygen extraction from blood, and in cardiovascular function that occur with exercise training. Cross-sectional studies of aerobic exercise trained individuals are conflicting and have reported both reduced pressure from wave reflections (198;206;207) and increased pressure from wave reflections (208;209). 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 due to an increased 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 (197;210) or no change (211). 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 (212) and improvements in LV contractility (213) 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 lowers LV afterload (static and dynamic components) and heart rate, enhances quality of life and reduces morbidity and mortality from cardiovascular events (214). In a recent review of the effects of diet and exercise on arterial

stiffness in patients with elevated cardio-metabolic risk from hypertension, signs of atherosclerosis, or kidney disease, Sacre and colleagues noted that these non-drug interventions can improve arterial stiffness by several mechanisms (215). Aerobic exercise may do so through improving vascular smooth muscle cell relaxation through increased nitric oxide bioavailability, and reductions in oxidant stress and inflammation. Among dietary approaches, reduced sodium intake has so far shown that while it is associated with reductions in pulse wave velocity, these seem due largely to the changes in blood pressure that occur (though others have found a reduction in PWV independent of blood pressure changes (216)). They (i.e. Sacre et al) 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, 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 (217).

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 (218). 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 (219). Resistance exercise training was initially shown to increase pressure from wave reflections (220) with subsequent studies noting no effect (212;221–225).

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

Section 5. Arterial Stiffness in Children

- **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 CV risk factors in children are too young to provide data linking CV risk factor levels measured in childhood to hard CV events in adulthood (226).

However, there are correlations between known adult CV risk factors, high-risk conditions, such as chronic kidney disease (CKD) and diabetes mellitus (DM), and novel risk factors with intermediate non-invasive measures of vascular health, which are linked to hard events in adults. In this section, we will discuss the current evidence, with reference to the previous AHA manuscript on non-invasive measures in children (227).

Arterial stiffness, CV risk factors, and high risk disease states in pediatrics

There are now sufficient data from studies such as the Bogalusa Heart Study, to link CV risk factors measured in youth such as blood pressure (BP) directly to estimate PWV in

adulthood (228). The CV Risk in Young Finns study has also demonstrated higher adult PWV with clustering of risk factors in youth, such as in the metabolic syndrome (229). Conversely, clustering of advantageous risk factors (fruit and vegetable consumption) is associated with a lower PWV as an adult (230). Low birth weight was associated with higher PWV in adulthood in one study that examined baPWV (231), but was not found in a study that examined cfPWV (232). These differences highlight the importance of standardization of measurements, and that indices of stiffness are not always interchangeable as 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 gender differences in PWV. One study found higher carotid-femoral (cf) and femoral-dorsalis pedis (fd) PWV in females before puberty with the difference for cfPWV disappearing after maturation whereas fdPWV was higher in males post-puberty (233). Using baPWV, higher values were found in males regardless of maturation level (234).

Traditional CV risk factors have been found to influence PWV in youth. Children with elevated LDL-cholesterol had significantly higher PWV compared to controls (4.72 ± 0.72 m/sec vs 3.66 ± 0.55 m/sec) (235) and PWV increases across tertiles of TG/HDL ratio, a lipid parameter that reflects burden of small dense LDL particles (236). Higher PWV compared to controls was found in adolescents with a family history of hypertension (237;238), pre-hypertension (239–241), and sustained hypertension (239;240). Other CV risk factors such as psycho-social stress (242–244), smoking (245), low physical fitness (246;247), or physical inactivity (248;249), and low dairy intake (250) 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 over 600 subjects each demonstrated higher PWV in obese adolescents as compared to their lean counterparts (251) and the effect of obesity was independent of other CV risk factors (252). Obesity-related metabolic syndrome clustering was also shown to result in higher PWV (253). However, insulin resistance appears to play an independent role only for baPWV (254;255) and not cfPWV (256).

Since CV risk factors influence PWV, it is not surprising that higher PWV is found in children and adolescents with high-risk conditions. Youth with type 2 DM have higher PWV than both their lean and obese counterparts (252). Surprisingly, subjects with type 2 DM have higher PWV than those with type 1 DM despite a shorter duration of disease (257). In a study of 535 subjects with type 1 DM and 60 with type 2 DM, it was found that the higher PWV in type 2 DM was largely explained by increased central adiposity and higher BP (257).

Pediatric patients with renal disease also demonstrate increased arterial stiffness, a potential mechanism for the observed increased in CV events in adults with kidney disease (258). Children on dialysis have higher PWV than less severely affected patients (259) and controls

(260). Unfortunately, these adverse vascular changes may not normalize after renal transplantation (261–263). However, children with glomerulonephritis and increased PWV did see normalization with recovery (264). For this reason, there is hope that treatment of inflammatory vasculitis such as seen in HIV-infection (265), polyarteritis nodosa (266), and Kawasaki's disease (267), may result in 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 transplant (268). 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 (269–271) and in youth after arterial switch operation for transposition of the great vessels (272). The largest amount of work has been done in patients after repair of coarctation of the aorta, due to heightened concern for the role of arterial stiffness, manifest as increased PWV, in late complications such as hypertension (273–276) and premature CV disease (277). Data on other inherited disorders associated with increased arterial stiffness are less clear. One study of Marfan's syndrome patients found higher PWV compared to controls (176), while another small study of Marfan's (N= 10 cases and 10 controls) (278) and one of youth with neurofibromatosis type 1 (279), found no differences. Clearly, larger studies of PWV in pediatric patients with these high-risk conditions should be conducted.

The use of these non-invasive intermediate endpoints to better risk-stratify youth is essential as data linking childhood measures of CV risk factors to hard CV events in adults are lacking. Further studies correlating risk factors to vascular damage to target organ damage like LVH will provide evidence to pediatric practitioners faced with the challenge of implementing aggressive drug therapy in high risk children. Assessing PWV in 'normal' children may also provide an ideal platform to identify novel mechanisms driving stiffness as 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 (234;280–282)**,** including large and small artery compliance (283). Using MRI, Voges found a decrease in descending aorta distensibility and increase in PWV starting at age 2.3 years (284). 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 (284). 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 (285). 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 (233), Fischer found sex differences in PWV both pre- and

post-puberty (281), and Voges found no difference (284). 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 Augmentation Index (AIx), ambulatory arterial stiffness index, normal values in youth, and technical considerations for measurement in children are also discussed in the Online Supplement Section 5.

Section 6. Validation of Arterial Stiffness devices

Recommendation

- **6.1** You should determine the distance for the carotid-femoral PWV by subtracting the suprasternal-notch to carotid site distance from the suprasternal-notch to femoral site distance, or by multiplying the total directly measured distance by 0.8 (Class I, Level of Evidence B) (14).
- **6.2** We recommend that you perform validation studies against invasive measurements; where this is not possible they should be validated against a non-invasive 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 non-invasive PWV estimation.

Invasive aortic PWV—This measurement has the advantage of being a simple, straightforward, precise, reproducible technique (measuring transit time (TT) simultaneously or ECG triggered and travel distance (TD) between two measurement sites (14). 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 (14;286–291). So far, one study investigated its relationship to clinical outcomes (288).

Magnetic resonance imaging based aortic PWV—With this technique, TD can be measured very accurately due to 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 somewhat lower in comparison to the other techniques, although this has been improved recently (292). The reproducibility and the accuracy with respect to invasive measurements may also depend on the methods used to determine TT (293), 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.

Simultaneous non-invasive 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 (45).

Can dedicated devices for the measurement of cfPWV be recommended as a non-invasive 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 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 (294). 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 (e.g. BMI > 30 kg/m2, 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 of systematic errors. The results of device/method validation studies should be presented using the method of Bland and Altman (295), 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 of, and the difference between, the two methods/devices and includes +/− 2 standard deviations as boundaries. Excellent, acceptable and poor accuracy may be defined as shown in Table 2 (294). 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.

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 (25). 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 mean difference of 0.02 m/s and SD of 0.61 m/s.

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 (296). 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 (297). 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 (297), 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. This is, thus, not a simple unidirectional path length (137), thereby rendering all determinations of the "real" travelled path length somewhat elusive. Even sophisticated MRI-based distance 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, PWV in the carotid artery can be 2–3 m/sec higher than in the aortic arch (298), and in humans the differences between aortic and carotid stiffness are higher in patients with hypertension and diabetes (299). Whether these differences can affect the actual cfPWV by 2% or up to 10% has been recently discussed (300). However, some standardization is obviously necessary, and comparisons of cfPWV with invasive PWV and MRI-PWV have been made. In 135 patients undergoing invasive coronary angiography, the "subtraction method" (suprasternal notch (SSN)-femoral artery minus SSN-carotid artery) resulted in the smallest differences (0.2 m/sec) between invasive aoPWV and non-invasive cfPWW (14), 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 (297). 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 (301). 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 (139), 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. Additionally, the use of calipers may improve distance measurements particularly in overweight or obese subjects (302;303).

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

Validation of devices to measure brachial-ankle Pulse Wave Velocity (baPWV)—Repeatability and reproducibility can be investigated as usual, and such studies have been performed successfully (36;44). 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 Asian individuals, which may differ from Western populations. Although the travelled path with baPWV clearly differs from pure aortic (invasive) PWV and also from cfPWV through the inclusion of longer segments of muscular arteries, comparisons with invasive PWV (36) and cfPWV (304) have been made, showing a high degree of correlation. For non-invasive validation studies, systems that have been shown to predict cardiovascular outcomes should be used such as the VP1000 ® (Omron Healthcare, Japan) and the Vasera (Fukuda Denshi, Japan) (see 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 waveforms 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/or non-invasive validation against gold-standard devices measuring cfPWV. So far, invasive validation has been performed successfully for the Arteriograph © (Arteriomed, Hungary) (305) and the Mobil-O-Graph © (I.E.M., Germany) (40). Clinical validation, i.e. the prediction of cardiovascular events, is pending for the Arteriograph. One small study in patients with chronic kidney disease, NKF stages 2–4, has already shown the independent prognostic value of an estimated aortic PWV (measured with the Mobil-O-Graph device) with respect to mortality (306).

Section 7. Factors confounding arterial stiffness measures and practical interpretation of values

Recommendations

- **7.1** Mean arterial pressure (MAP) and heart rate should be recorded at the time of an arterial stiffness measurement and taken into consideration when analyzing PWV data as potential confounders (Class I, Level of Evidence B) (15;16).
- **7.2** The following are recommendations to enhance uniformity in arterial stiffness investigations:
  - i. Clearly state the sites of measurement in the Methods section, for example “carotid-femoral” (Class I, Level of Evidence C);
  - ii. It is reasonable to report how the distance measurement was performed in the Methods section (Class IIa, Level of Evidence C);
  - iii. It is reasonable to use calipers to obtain surface measurements to calculate distance for PWV (Class IIa, Level of Evidence C);
  - iv. We recommend that you perform arterial stiffness measurements, in duplicate, supine after a minimum of 10 minutes of rest, controlling the environmental noise and temperature as much as possible; you should repeat the arterial stiffness measurement a third time if the difference in the two measurements is more than 0.5 m/sec using the median value (Class I, Level of Evidence C);

- v. You should ensure that operators performing arterial stiffness measurements are familiar with the equipment, have been trained in the techniques, and have demonstrated consistently reproducible results (Class I, Level of Evidence C).

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

Physiological confounders—The most significant physiological variable affecting arterial stiffness is the vessel distending pressure (mean arterial pressure; MAP) (15;18;307;308). In contrast, pulse pressure 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 non-linear manner. Therefore, the measured value of stiffness will depend on, or be confounded by, the mean arterial pressure, which should be taken into consideration. This is particularly relevant when comparing populations with different blood pressures or when investigating the effects of anti-hypertensive agents.

The relationship between heart rate and arterial stiffness is less well defined, with acute studies showing positive associations (16;309;310), no association (311;312), or even inverse associations (313) 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 MAP. Nevertheless, a recent study (314) 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 MAP values. Since blood pressure and heart rate vary considerably both within and between individuals, both should be taken into consideration when undertaking measurements of arterial stiffness.

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 2–4 hours prior to 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 non-invasive assessment of arterial stiffness (45), often arterial stiffness is measured in alternative (or additional) vascular beds. For example, several noninvasive commercial devices assess baPWV. 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. It is important to

recognize that indices are not necessarily interchangeable, either physiologically or prognostically, and it is important to clearly state the methodology used to assess PWV.

Even within a vascular bed, PWV may vary depending on the specific device that is used to measure PWV. For example, Millasseau et al (315) 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 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%.

Perhaps the most important methodological confounder of pulse wave velocity measurements is calculation of the wave travel distance (see Section 6). cfPWV 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 - up to 30% in one study (316), and the measurement method and vascular territory should be clearly stated in the manuscript.

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 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), which better corresponds to the true anatomical distance assessed by MRI (301). Weber et al also found that the subtraction method was more closely related to true distance and that carotid-femoral PWV determined with the device and the subtracted distance corresponded best with invasive assessment of PWV (14). Although a recent expert consensus document advised distance should be calculated by multiplying the direct distance by 0.8 and conversion algorithms between the two methods have been developed (317), these are likely to introduce further error. Therefore, the method of distance calculation should be clearly stated, and the subtracted distance is more anatomically true (see 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 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.

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 to determine competency. 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.

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 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 carotid-femoral 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 (318;319). Much larger meta-analyses of individual patient data will be required in the future to be sure that decreases in aortic PWV following therapy are truly blood pressure independent. The cellular/molecular pro-inflammatory mechanisms driven by Ang 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 (320).

Future needs in investigating the import of arterial stiffness should include addressing questions such as:

- 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 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 is it safe, to unstiffen the aorta independent of blood pressure reduction?

- Can the similarities in aging and stiffening of the arterial wall in animal models be used to guide human intervention trials; 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 de-stiffening approach from a reduction in blood pressure?
- Are there non-drug interventions that are likely to benefit arterial stiffening processes? At what age should such interventions be introduced?

Many of the above will be facilitated by the development of cuff based systems which will allow for the measurement of hemodynamic parameters such as cfPWV, central blood pressure and AIx with as much ease and operator independence as oscillometric sphygmomanometry. Such systems have already been validated, and, in addition, have the facility for 24hr ambulatory assessment of central blood pressure (such as the Mobil-O-Graph © covered in Section 2). A logical progression would be to measure cfPWV using non cuff based systems and such systems are already in development (321).

The establishment of international reference norms for PWV across age and blood pressure strata (139), increasing recognition of the importance of central arterial stiffness as a consequence of aging and co-morbidities (22;105), potential improvements in understanding study outcome mechanisms when these measurements are incorporated (59;196), recognition of the limitations of these measurements coupled with 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. These include:

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

As this summary statement was nearing final draft stage a large patient-level (n=17,635) meta-analysis of arterial stiffness was published (3). This lends more support to the growing interest in arterial stiffness.

Overall Summary

Measuring arterial stiffness has been established clinically through longitudinal studies where it has independently predicted death, as well as standard cardiovascular endpoints. 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 blood pressure

levels in clinical medicine and clinical research is an ongoing journey, and its indication for use in the clinic requires further study. The authors hope this Summary Statement represents a forward step in this journey.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

ACE	Angiotensin converting enzyme
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)
CKD	Chronic Kidney Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate (typically from the MDRD equation; mL/min/1.73m^2)
ECG	Electrocardiogram
Ea	Arterial Elastance (a measure that relates end systolic pressure to LV stroke volume)
EECP	Enhanced External Counter-Pulsation
Einc	Elastic Modulus (dynes/cm^2)
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESRD	End Stage Renal Disease
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)
HF	Heart Failure
IDI	Integrated Discrimination Improvement (statistics procedure)
LDL	Low Density Lipoprotein
LOE	Level of Evidence
LV	Left Ventricle
LVH	Left Ventricle Hypertrophy
LVOT	Left Ventricle Outflow Tract
MAP	Mean Arterial Pressure (mmHg)
MRI	Magnetic Resonance Imaging
NIR	Net Reclassification Index (ratio)
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)
RM	Reflected wave Magnitude (mmHg)
SBP	Systolic Blood Pressure
SD	Standard Deviation
SVR	Systemic Vascular Resistance (dynes-second/cm^5)
TD	Travel Distance (millimeters or meters)
TT	Transit Time (milliseconds, or seconds)
VENC	Velocity-Encoding Sensitivity (an MRI technique to measure flow velocity)
Zc	Characteristic aortic impedance (also called Zo; measures aortic pressure-flow relationship; ((mmHg*sec)/mL)

Reference List

1. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens. 2002; 15(5):426–444. [PubMed: 12022246]
2. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010; 55(13):1318–1327. [PubMed: 20338492]
3. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell

K, Verbeke F, Wang KL, Webb DJ, Hansen TW, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2013

4. Kato A, Takita T, Furuhashi M, Maruyama Y, Miyajima H, Kumagai H. Brachial-ankle pulse wave velocity and the cardio-ankle vascular index as a predictor of cardiovascular outcomes in patients on regular hemodialysis. Ther Apher Dial. 2012; 16(3):232–241. [PubMed: 22607566]
5. Vlachopoulos C, Aznaouridis K, Terentes-Printzios D, Ioakeimidis N, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with brachial-ankle elasticity index: a systematic review and meta-analysis. Hypertension. 2012; 60(2):556–562. [PubMed: 22733468]
6. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension. 2005; 45(4): 592–596. [PubMed: 15753232]
7. Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: part 1: pressure and flow measurements and basic principles of wave conduction and reflection. Hypertension. 2010; 56(4): 555–562. [PubMed: 20733089]
8. Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: part 2: arterial pressure-flow and pressure-volume relations in humans. Hypertension. 2010; 56(4):563–570. [PubMed: 20733088]
9. Chirinos JA, Rietzschel ER, Shiva-Kumar P, De Buyzere ML, Zamani P, Claessens T, Geraci S, Konda P, De BD, Akers SR, Gillebert TC, Segers P. Effective Arterial Elastance Is Insensitive to Pulsatile Arterial Load. Hypertension. 2014
10. Segers P, Stergiopulos N, Westerhof N. Relation of effective arterial elastance to arterial system properties. Am J Physiol Heart Circ Physiol. 2002; 282(3):H1041–H1046. [PubMed: 11834502]
11. Chirinos JA, Kips JG, Jacobs DR Jr, Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial Wave Reflections and Incident Cardiovascular Events and Heart Failure: MESA (Multiethnic Study of Atherosclerosis). J Am Coll Cardiol. 2012; 60(21):2170–2177. [PubMed: 23103044]
12. Wang KL, Cheng HM, Sung SH, Chuang SY, Li CH, Spurgeon HA, Ting CT, Najjar SS, Lakatta EG, Yin FC, Chou P, Chen CH. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. Hypertension. 2010; 55(3): 799–805. [PubMed: 20065155]
13. Weber T, Wassertheurer S, Rammer M, Haiden A, Hametner B, Eber B. Wave reflections, assessed with a novel method for pulse wave separation, are associated with end-organ damage and clinical outcomes. Hypertension. 2012; 60(2):534–541. [PubMed: 22585948]
14. Weber T, Ammer M, Rammer M, Adji A, O'Rourke MF, Wassertheurer S, Rosenkranz S, Eber B. Noninvasive determination of carotid-femoral pulse wave velocity depends critically on assessment of travel distance: a comparison with invasive measurement. J Hypertens. 2009; 27(8): 1624–1630. [PubMed: 19531964]
15. Kim EJ, Park CG, Park JS, Suh SY, Choi CU, Kim JW, Kim SH, Lim HE, Rha SW, Seo HS, Oh DJ. Relationship between blood pressure parameters and pulse wave velocity in normotensive and hypertensive subjects: invasive study. J Hum Hypertens. 2007; 21(2):141–148. [PubMed: 17136108]
16. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. Hypertension. 2002; 39(6):1083–1087. [PubMed: 12052846]
17. Chirinos JA. Arterial stiffness: basic concepts and measurement techniques. J Cardiovasc Transl Res. 2012; 5(3):243–255. [PubMed: 22447229]
18. Nichols, WW.; O'Rourke, MF.; Vlachopoulos, C. McDonald's blood flow in arteries. 6. London: Hodder Arnold; 2011.
19. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol. 2000; 525(Pt 1): 263–270. [PubMed: 10811742]
20. Wolinksy H, Glagov S. Structural Basis for the Static Mechanical Properties of the Aortic Media. Circ Res. 1964; 14:400–413. [PubMed: 14156860]

21. Avolio A, Butlin M, Liu YY, Viegas K, Avadhanam B, Linday G. Regulation of arterial stiffness: cellular, molecular and neurogenic mechanisms. Artery Research. 2013; 5:122–127.
22. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a “set up” for vascular disease. Circulation. 2003; 107(1):139–146. [PubMed: 12515756]
23. McEniery CM, Spratt M, Munnery M, Yarnell J, Lowe GD, Rumley A, Gallacher J, Ben-Shlomo Y, Cockcroft JR, Wilkinson IB. An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly prospective study. Hypertension. 2010; 56(1):36–43. [PubMed: 20530296]
24. Townsend RR, Wimmer NJ, Chirinos JA, Parsa A, Weir M, Perumal K, Lash JP, Chen J, Steigerwalt SP, Flack J, Go AS, Rafey M, Rahman M, Sheridan A, Gadegbeku CA, Robinson NA, Joffe M. Aortic PWV in chronic kidney disease: a CRIC ancillary study. Am J Hypertens. 2010; 23(3):282–289. [PubMed: 20019670]
25. Butlin M, Qasem A, Battista F, Bozec E, McEniery CM, Millet-Amaury E, Pucci G, Wilkinson IB, Schillaci G, Boutouyrie P, Avolio AP. Carotid-femoral pulse wave velocity assessment using novel cuff-based techniques: comparison with tonometric measurement. J Hypertens. 2013; 31(11):2237–2243. [PubMed: 24077246]
26. Wimmer NJ, Townsend RR, Joffee MM, Lash JP, Go AS. CRIC Study Investigators. Correlation between pulse wave velocity and other measures of arterial stiffness in chronic kidney disease. Clinical Nephrology. 2007; 68(3):133–143. [PubMed: 17915615]
27. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension. 1995; 26(3):485–490. [PubMed: 7649586]
28. Pereira T, Maldonado J. Comparative study of two generations of the Complior device for aortic pulse wave velocity measurements. Blood Press Monit. 2010; 15(6):316–321. [PubMed: 20838328]
29. Miljkovic D, Perret-Guillaume C, Alla F, Salvi P, Erpelding ML, Benetos A. Correlation between peripheral blood pressure and pulse-wave velocity values in the institutionalized elderly persons 80 years of age and older: the PARTAGE study. Am J Hypertens. 2013; 26(2):163–173. [PubMed: 23382400]
30. Salvi P, Lio G, Labat C, Ricci E, Pannier B, Benetos A. Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the PulsePen device. J Hypertens. 2004; 22(12):2285–2293. [PubMed: 15614022]
31. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation. 2010; 121(4):505–511. [PubMed: 20083680]
32. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. Brain. 2011; 134(Pt 11):3398–3407. [PubMed: 22075523]
33. Tomiyama H, Tanaka H, Hashimoto H, Matsumoto C, Odaira M, Yamada J, Yoshida M, Shiina K, Nagata M, Yamashina A. Arterial stiffness and declines in individuals with normal renal function/early chronic kidney disease. Atherosclerosis. 2010; 212(1):345–350. [PubMed: 20594557]
34. Matsuoka O, Otsuka K, Murakami S, Hotta N, Yamanaka G, Kubo Y, Yamanaka T, Shinagawa M, Nunoda S, Nishimura Y, Shibata K, Saitoh H, Nishinaga M, Ishine M, Wada T, Okumiya K, Matsubayashi K, Yano S, Ichihara K, Cornelissen G, Halberg F, Ozawa T. Arterial stiffness independently predicts cardiovascular events in an elderly community -- Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study. Biomed Pharmacother. 2005; 59 (Suppl 1):S40–S44. [PubMed: 16275505]
35. Turin TC, Kita Y, Rumana N, Takashima N, Kadota A, Matsui K, Sugihara H, Morita Y, Nakamura Y, Miura K, Ueshima H. Brachial-ankle pulse wave velocity predicts all-cause mortality in the general population: findings from the Takashima study, Japan. Hypertens Res. 2010; 33(9):922–925. [PubMed: 20555327]

36. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res. 2002; 25(3):359–364. [PubMed: 12135313]

37. Wei W, Tolle M, Zidek W, van der Giet M. Validation of the mobil-O-Graph: 24 h-blood pressure measurement device. Blood Press Monit. 2010; 15(4):225–228. [PubMed: 20216407]

38. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, Kropf J, Eber B. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension. 2011; 58(5):825–832. [PubMed: 21911710]

39. Luzardo L, Lujambio I, Sottolano M, da RA, Thijs L, Noboa O, Staessen JA, Boggia J. 24-h ambulatory recording of aortic pulse wave velocity and central systolic augmentation: a feasibility study. Hypertens Res. 2012; 35(10):980–987. [PubMed: 22622282]

40. Hametner B, Wassertheurer S, Kropf J, Mayer C, Eber B, Weber T. Oscillometric estimation of aortic pulse wave velocity: comparison with intra-aortic catheter measurements. Blood Press Monit. 2013; 18(3):173–176. [PubMed: 23571229]

41. Papaioannou TG, Argyris A, Protogerou AD, Vrachatis D, Nasothimiou EG, Sfikakis PP, Stergiou GS, Stefanadis CI. Non-invasive 24 hour ambulatory monitoring of aortic wave reflection and arterial stiffness by a novel oscillometric device: the first feasibility and reproducibility study. Int J Cardiol. 2013; 169(1):57–61. [PubMed: 24063914]

42. Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, Miyashita Y, Saiki A, Takahashi M, Suzuki K, Takata M. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. J Atheroscler Thromb. 2011; 18(11):924–938. [PubMed: 21628839]

43. Yamamoto N, Yamanaka G, Ishikawa M, Takasugi E, Murakami S, Yamanaka T, Ishine M, Matsubayashi K, Hanafusa T, Otsuka K. Cardio-ankle vascular index as a predictor of cognitive impairment in community-dwelling elderly people: four-year follow-up. Dement Geriatr Cogn Disord. 2009; 28(2):153–158. [PubMed: 19696483]

44. Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O, Tei C. Clinical significance and reproducibility of new arterial distensibility index. Circ J. 2007; 71(1):89–94. [PubMed: 17186984]

45. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006; 27(21):2588–2605. [PubMed: 17000623]

46. Hoeks AP, Brands PJ, Smeets FA, Reneman RS. Assessment of the distensibility of superficial arteries. Ultrasound Med Biol. 1990; 16(2):121–128. [PubMed: 2183458]

47. Calabia J, Torguet P, Garcia M, Garcia I, Martin N, Guasch B, Faur D, Valles M. Doppler ultrasound in the measurement of pulse wave velocity: agreement with the Complior method. Cardiovasc Ultrasound. 2011; 9:13. [PubMed: 21496271]

48. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation. 2002; 106(16):2085–2090. [PubMed: 12379578]

49. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation. 2005; 111(25):3384–3390. [PubMed: 15967850]

50. Wright JS, Cruickshank JK, Kontis S, Dore C, Gosling RG. Aortic compliance measured by non-invasive Doppler ultrasound: description of a method and its reproducibility. Clin Sci (Lond). 1990; 78(5):463–468. [PubMed: 2162271]

51. Sutton-Tyrrell K, Mackey RH, Holubkov R, Vaitkevicius PV, Spurgeon HA, Lakatta EG. Measurement variation of aortic pulse wave velocity in the elderly. Am J Hypertens. 2001; 14(5 Pt 1):463–468. [PubMed: 11368468]

52. Gatehouse PD, Keegan J, Crowe LA, Masood S, Mohiaddin RH, Kreitner KF, Firmin DN. Applications of phase-contrast flow and velocity imaging in cardiovascular MRI. Eur Radiol. 2005; 15(10):2172–2184. [PubMed: 16003509]

53. Gatehouse PD, Rolf MP, Graves MJ, Hofman MB, Totman J, Werner B, Quest RA, Liu Y, von SJ, Dieringer M, Firmin DN, van RA, Lombardi M, Schwitter J, Schulz-Menger J, Kilner PJ. Flow measurement by cardiovascular magnetic resonance: a multi-centre multi-vendor study of background phase offset errors that can compromise the accuracy of derived regurgitant or shunt flow measurements. J Cardiovasc Magn Reson. 2010; 12:5. [PubMed: 20074359]
54. Langham MC, Li C, Magland JF, Wehrli FW. Nontriggered MRI quantification of aortic pulse-wave velocity. Magn Reson Med. 2011; 65(3):750–755. [PubMed: 20882637]
55. Itskovich VV, Kraft KA, Fei DY. Rapid aortic wave velocity measurement with MR imaging. Radiology. 2001; 219(2):551–557. [PubMed: 11323487]
56. Macgowan CK, Henkelman RM, Wood ML. Pulse-wave velocity measured in one heartbeat using MR tagging. Magn Reson Med. 2002; 48(1):115–121. [PubMed: 12111938]
57. Shao X, Fei DY, Kraft KA. Rapid measurement of pulse wave velocity via multisite flow displacement. Magn Reson Med. 2004; 52(6):1351–1357. [PubMed: 15562479]
58. Grotenhuis HB, Westenberg JJ, Steendijk P, van der Geest RJ, Ottenkamp J, Bax JJ, Jukema JW, de RA. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. J Magn Reson Imaging. 2009; 30(3):521–526. [PubMed: 19711407]
59. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation. 2001; 103(7):987–992. [PubMed: 11181474]
60. Orlova IA, Nuraliev EY, Yarovaya EB, Ageev FT. Prognostic value of changes in arterial stiffness in men with coronary artery disease. Vasc Health Risk Manag. 2010; 6:1015–1021. [PubMed: 21127698]
61. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension. 2009; 54(6): 1328–1336. [PubMed: 19884567]
62. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012; 308(9):875–881. [PubMed: 22948697]
63. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, Heiss G. Arterial stiffness and the development of hypertension. The ARIC study Hypertension. 1999; 34(2):201–206. [PubMed: 10454441]
64. Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sonoda H, Sato K, Kimura G. Brachial-ankle pulse wave velocity predicts increase in blood pressure and onset of hypertension. Am J Hypertens. 2011; 24(6):667–673. [PubMed: 21331056]
65. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension. 2005; 45(3):426–431. [PubMed: 15710784]
66. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, Spurgeon HP, Ferrucci L, Lakatta EG. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol. 2008; 51(14):1377–1383. [PubMed: 18387440]
67. Mattace-Raso FU, van den Meiracker AH, Bos WJ, van der Cammen TJ, Westerhof BE, Elias-Smale S, Reneman RS, Hoeks AP, Hofman A, Witteman JC. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: the Rotterdam Study. J Hypertens. 2007; 25(7):1421–1426. [PubMed: 17563564]
68. Mattace-Raso FU, van der Cammen TJ, Knetsch AM, van den Meiracker AH, Schalekamp MA, Hofman A, Witteman JC. Arterial stiffness as the candidate underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the Rotterdam Study. J Hypertens. 2006; 24(2):339–344. [PubMed: 16508582]
69. Protogerou AD, Stergiou GS, Lourida P, Achimastos A. Arterial stiffness and orthostatic blood pressure changes in untreated and treated hypertensive subjects. J Am Soc Hypertens. 2008; 2(5): 372–377. [PubMed: 20409918]

70. Kingwell BA, Cameron JD, Gillies KJ, Jennings GL, Dart AM. Arterial compliance may influence baroreflex function in athletes and hypertensives. Am J Physiol. 1995; 268(1 Pt 2):H411–H418. [PubMed: 7840291]
71. Virtanen R, Jula A, Huikuri H, Kuusela T, Helenius H, Ylitalo A, Voipio-Pulkki LM, Kauma H, Kesaniemi YA, Airaksinen J. Increased pulse pressure is associated with reduced baroreflex sensitivity. J Hum Hypertens. 2004; 18(4):247–252. [PubMed: 15037873]
72. Okada Y, Galbreath MM, Shibata S, Jarvis SS, VanGundy TB, Meier RL, Vongpatanasin W, Levine BD, Fu Q. Relationship between sympathetic baroreflex sensitivity and arterial stiffness in elderly men and women. Hypertension. 2012; 59(1):98–104. [PubMed: 22106403]
73. Thanassoulis G, Lyass A, Benjamin EJ, Larson MG, Vita JA, Levy D, Hamburg NM, Widlansky ME, O'Donnell CJ, Mitchell GF, Vasan RS. Relations of exercise blood pressure response to cardiovascular risk factors and vascular function in the Framingham Heart Study. Circulation. 2012; 125(23):2836–2843. [PubMed: 22572915]
74. Kelly RP, Tunin R, Kass DA. Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. Circ Res. 1992; 71(3):490–502. [PubMed: 1386792]
75. Kass DA, Saeki A, Tunin RS, Recchia FA. Adverse influence of systemic vascular stiffening on cardiac dysfunction and adaptation to acute coronary occlusion. Circulation. 1996; 93(8):1533–1541. [PubMed: 8608622]
76. Abhayaratna WP, Srikusalanukul W, Budge MM. Aortic stiffness for the detection of preclinical left ventricular diastolic dysfunction: pulse wave velocity versus pulse pressure. J Hypertens. 2008; 26(4):758–764. [PubMed: 18327086]
77. Russo C, Jin Z, Palmieri V, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Arterial stiffness and wave reflection: sex differences and relationship with left ventricular diastolic function. Hypertension. 2012; 60(2):362–368. [PubMed: 22753223]
78. Dart AM, Kingwell BA. Pulse pressure--a review of mechanisms and clinical relevance. J Am Coll Cardiol. 2001; 37(4):975–984. [PubMed: 11263624]
79. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation. 1989; 80(1):78–86. [PubMed: 2610739]
80. Stefanadis C, Wooley CF, Bush CA, Kolibash AJ, Boudoulas H. Aortic distensibility abnormalities in coronary artery disease. Am J Cardiol. 1987; 59(15):1300–1304. [PubMed: 3591683]
81. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, Hoeks AP, van der Kuip DA, Hofman A, Witteman JC. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. Stroke. 2001; 32(2):454–460. [PubMed: 11157182]
82. Hori M, Inoue M, Kitakaze M, Tsujioka K, Ishida Y, Fukunami M, Nakajima S, Kitabatake A, Abe H. Loading sequence is a major determinant of afterload-dependent relaxation in intact canine heart. Am J Physiol. 1985; 249(4 Pt 2):H747–H754. [PubMed: 4051013]
83. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation. 2003; 107(5):714–720. [PubMed: 12578874]
84. Kohno F, Kumada T, Kambayashi M, Hayashida W, Ishikawa N, Sasayama S. Change in aortic end-systolic pressure by alterations in loading sequence and its relation to left ventricular isovolumic relaxation. Circulation. 1996; 93(11):2080–2087. [PubMed: 8640985]
85. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation. 2005; 112(15):2254–2262. [PubMed: 16203909]
86. Weber T, Wassertheurer S, O'Rourke MF, Haiden A, Zweiker R, Rammer M, Hametner B, Eber B. Pulsatile hemodynamics in patients with exertional dyspnea: potentially of value in the diagnostic evaluation of suspected heart failure with preserved ejection fraction. J Am Coll Cardiol. 2013; 61(18):1874–1883. [PubMed: 23500307]
87. Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG, D'Agostino RB Sr, Kannel WB, Levy D, Benjamin EJ. Pulse pressure and risk of new-onset atrial fibrillation. JAMA. 2007; 297(7):709–715. [PubMed: 17312290]

88. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. JAMA. 1999; 281(7):634–639. [PubMed: 10029125]

89. Desai AS, Mitchell GF, Fang JC, Creager MA. Central aortic stiffness is increased in patients with heart failure and preserved ejection fraction. J Card Fail. 2009; 15(8):658–664. [PubMed: 19786254]

90. Mitchell GF, Tardif JC, Arnold JM, Marchiori G, O'Brien TX, Dunlap ME, Pfeffer MA. Pulsatile hemodynamics in congestive heart failure. Hypertension. 2001; 38(6):1433–1439. [PubMed: 11751731]

91. Mitchell GF, Arnold JM, Dunlap ME, O'Brien TX, Marchiori G, Warner E, Granger CB, Desai SS, Pfeffer MA. Pulsatile hemodynamic effects of candesartan in patients with chronic heart failure: the CHARM Program. Eur J Heart Fail. 2006; 8(2):191–197. [PubMed: 16188495]

92. Wilkinson IB, McEniery CM, Cockcroft JR. Arteriosclerosis and atherosclerosis: guilty by association. Hypertension. 2009; 54(6):1213–1215. [PubMed: 19884560]

93. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004; 43(6):1239–1245. [PubMed: 15123572]

94. Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. Circulation. 2010; 122(14):1379–1386. [PubMed: 20855656]

95. Mitchell GF, Vita JA, Larson MG, Parise H, Keyes MJ, Warner E, Vasan RS, Levy D, Benjamin EJ. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. Circulation. 2005; 112(24):3722–3728. [PubMed: 16330686]

96. Baumbach GL, Siems JE, Heistad DD. Effects of local reduction in pressure on distensibility and composition of cerebral arterioles. Circ Res. 1991; 68(2):338–351. [PubMed: 1991342]

97. Baumbach GL. Effects of increased pulse pressure on cerebral arterioles. Hypertension. 1996; 27(2):159–167. [PubMed: 8567036]

98. Christensen KL. Reducing pulse pressure in hypertension may normalize small artery structure. Hypertension. 1991; 18(6):722–727. [PubMed: 1835958]

99. James MA, Watt PA, Potter JF, Thurston H, Swales JD. Pulse pressure and resistance artery structure in the elderly. Hypertension. 1995; 26(2):301–306. [PubMed: 7635539]

100. Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, Bertacchini F, Stassaldi D, Gavazzi A, Porteri E, De CC, Agabiti-Rosei E. Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients. Hypertension. 2013; 61(1):130–136. [PubMed: 23150518]

101. Loutzenhiser R, Bidani A, Chilton L. Renal myogenic response: kinetic attributes and physiological role. Circ Res. 2002; 90(12):1316–1324. [PubMed: 12089070]

102. Loutzenhiser R, Griffin K, Williamson G, Bidani A. Renal autoregulation: new perspectives regarding the protective and regulatory roles of the underlying mechanisms. Am J Physiol Regul Integr Comp Physiol. 2006; 290(5):R1153–R1167. [PubMed: 16603656]

103. Mellander S, Arvidsson S. Possible 'dynamic' component in the myogenic vascular response related to pulse pressure distension. Acta Physiol Scand. 1974; 90(1):283–285. [PubMed: 4814541]

104. Shepherd AP. Effect of arterial pulse pressure and hypoxia on myogenic responses in the gut. Am J Physiol. 1978; 235(2):H157–H161. [PubMed: 686182]

105. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol. 2008; 105(5):1652–1660. [PubMed: 18772322]

106. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke. 2003; 34(5): 1203–1206. [PubMed: 12677025]

107. Domanski MJ, Davis BR, Pfeffer MA, Kastantin M, Mitchell GF. Isolated systolic hypertension : prognostic information provided by pulse pressure. Hypertension. 1999; 34(3):375–380. [PubMed: 10489379]
108. Lovett JK, Howard SC, Rothwell PM. Pulse pressure is independently associated with carotid plaque ulceration. J Hypertens. 2003; 21(9):1669–1676. [PubMed: 12923399]
109. Hashimoto J, Ito S. Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta: potential implication for retrograde embolic stroke in hypertension. Hypertension. 2013; 62(3):542–549. [PubMed: 23798349]
110. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010; 375(9718):895–905. [PubMed: 20226988]
111. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin JM, Lecompte T, Lacolley P, Benetos A, Zannad F. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke. 2009; 40(4):1229–1236. [PubMed: 19246701]
112. Scuteri A, Tesauro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. J Hypertens. 2007; 25(5):1035–1040. [PubMed: 17414668]
113. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, De Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension. 2008; 52(6):1120–1126. [PubMed: 18852384]
114. Brandts A, van Elderen SG, Westenberg JJ, van der Grond J, van Buchem MA, Huisman MV, Kroft LJ, Tamsma JT, de RA. Association of aortic arch pulse wave velocity with left ventricular mass and lacunar brain infarcts in hypertensive patients: assessment with MR imaging. Radiology. 2009; 253(3):681–688. [PubMed: 19864506]
115. van Elderen SG, Brandts A, Westenberg JJ, van der Grond J, Tamsma JT, van Buchem MA, Romijn JA, Kroft LJ, Smit JW, de RA. Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by magnetic resonance imaging. Eur Radiol. 2010; 20(5):1132–1138. [PubMed: 19915847]
116. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK. Arterial pulse wave velocity and cognition with advancing age. Hypertension. 2009; 53(4):668–673. [PubMed: 19237680]
117. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. Hypertension. 2008; 51(1):99–104. [PubMed: 18025297]
118. Hashimoto J, Aikawa T, Imai Y. Large artery stiffening as a link between cerebral lacunar infarction and renal albuminuria. Am J Hypertens. 2008; 21(12):1304–1309. [PubMed: 18802428]
119. Poels MM, van OM, Mattace-Raso FU, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study. Stroke. 2007; 38(3):888–892. [PubMed: 17272780]
120. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, DeCarli C, Au R, Himali JJ, Hamburg NM, Vita JA, Levy D, Larson MG, Benjamin E, Wolf PA, Vasan RS, Mitchell GF. Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology. 2013; 81:984–991. [PubMed: 23935179]
121. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011; 42(9):2672–2713. [PubMed: 21778438]
122. Baumann M, Pan CR, Roos M, von EM, Sollinger D, Lutz J, Heemann U. Pulsatile stress correlates with (micro-)albuminuria in renal transplant recipients. Transpl Int. 2010; 23(3):292–298. [PubMed: 19821953]

123. Hashimoto J, Ito S. Central pulse pressure and aortic stiffness determine renal hemodynamics: pathophysiological implication for microalbuminuria in hypertension. Hypertension. 2011; 58(5): 839–846. [PubMed: 21968753]

124. Doi Y, Iwashima Y, Yoshihara F, Kamide K, Hayashi S, Kubota Y, Nakamura S, Horio T, Kawano Y. Renal resistive index and cardiovascular and renal outcomes in essential hypertension. Hypertension. 2012; 60(3):770–777. [PubMed: 22824987]

125. Upadhyay A, Hwang SJ, Mitchell GF, Vasan RS, Vita JA, Stantchev PI, Meigs JB, Larson MG, Levy D, Benjamin EJ, Fox CS. Arterial stiffness in mild-to-moderate CKD. J Am Soc Nephrol. 2009; 20(9):2044–2053. [PubMed: 19608701]

126. Briet M, Bozec E, Laurent S, Fassot C, London GM, Jacquot C, Froissart M, Houillier P, Boutouyrie P. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. Kidney Int. 2006; 69(2):350–357. [PubMed: 16408126]

127. Lacy P, Carr SJ, O'Brien D, Fentum B, Williams B, Paul SK, Robinson TG. Reduced glomerular filtration rate in pre-dialysis non-diabetic chronic kidney disease patients is associated with impaired baroreceptor sensitivity and reduced vascular compliance. Clin Sci (Lond). 2006; 110(1):101–108. [PubMed: 16171454]

128. Mourad JJ, Pannier B, Blacher J, Rudnichi A, Benetos A, London GM, Safar ME. Creatinine clearance, pulse wave velocity, carotid compliance and essential hypertension. Kidney Int. 2001; 59(5):1834–1841. [PubMed: 11318954]

129. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. Am J Kidney Dis. 2005; 45(3):494–501. [PubMed: 15754271]

130. Yoshida M, Tomiyama H, Yamada J, Koji Y, Shiina K, Nagata M, Yamashina A. Relationships among renal function loss within the normal to mildly impaired range, arterial stiffness, inflammation, and oxidative stress. Clin J Am Soc Nephrol. 2007; 2(6):1118–1124. [PubMed: 17913969]

131. Hermans MM, Henry R, Dekker JM, Kooman JP, Kostense PJ, Nijpels G, Heine RJ, Stehouwer CD. Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: the Hoorn Study. J Am Soc Nephrol. 2007; 18(6):1942–1952. [PubMed: 17460143]

132. Verhave JC, Fesler P, Du CG, Ribstein J, Safar ME, Mimran A. Elevated pulse pressure is associated with low renal function in elderly patients with isolated systolic hypertension. Hypertension. 2005; 45(4):586–591. [PubMed: 15738348]

133. Stevens LA, Levey AS. Chronic kidney disease in the elderly--how to assess risk. N Engl J Med. 2005; 352(20):2122–2124. [PubMed: 15901867]

134. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med. 2006; 354(23):2473–2483. [PubMed: 16760447]

135. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem. 1992; 38(10):1933–1953. [PubMed: 1394976]

136. Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De CR, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HA, Viigimaa M, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van ZP, Viigimaa M, Waeber B, Williams B, Zamorano JL. The task force for the management of arterial hypertension of the European, Society of Hypertension, The task force for the management of arterial hypertension of the European, Society of Cardiology. . 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2007; 28(12):1462–1536. [PubMed: 17562668]

137. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De BT, Filipovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD, Schillaci G, Segers P, Vermeersch S, Weber T. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens. 2012; 30(3):445–448. [PubMed: 22278144]

138. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol. 2005; 46(9):1753–1760. [PubMed: 16256881]

139. The Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J. 2010; 31(19):2338–2350. [PubMed: 20530030]

140. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation. 1983; 68(1):50–58. [PubMed: 6851054]

141. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation. 1985; 71(2):202–210. [PubMed: 3965165]

142. Truswell AS, Kennelly BM, Hansen JD, Lee RB. Blood pressures of Kung bushmen in Northern Botswana. Am Heart J. 1972; 84(1):5–12. [PubMed: 5080283]

143. Mitchell GF. Clinical achievements of impedance analysis. Med Biol Eng Comput. 2009; 47(2): 153–163. [PubMed: 18853214]

144. Flack JM, Sica DA, Bakris G, Brown AL, Ferdinand KC, Grimm RH Jr, Hall WD, Jones WE, Kountz DS, Lea JP, Nasser S, Nesbitt SD, Saunders E, Scisney-Matlock M, Jamerson KA. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. Hypertension. 2010; 56(5):780–800. [PubMed: 20921433]

145. Namasivayam M, Adji A, O'Rourke MF. Influence of aortic pressure wave components determined noninvasively on myocardial oxygen demand in men and women. Hypertension. 2011; 57(2):193–200. [PubMed: 21173342]

146. Westerhof N, O'Rourke MF. Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. J Hypertens. 1995; 13(9):943–952. [PubMed: 8586828]

147. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, Kloch-Badelek M, Wilinski J, Curylo AM, Dudek D. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. Hypertension. 2008; 51(4): 848–855. [PubMed: 18268136]

148. Weber T, Auer J, Lamm G, O'Rourke MF, Eber B. Arterial stiffness, central blood pressures, and wave reflections in cardiomyopathy-implications for risk stratification. J Card Fail. 2007; 13(5): 353–359. [PubMed: 17602981]

149. Hashimoto J, Imai Y, O'Rourke MF. Indices of pulse wave analysis are better predictors of left ventricular mass reduction than cuff pressure. Am J Hypertens. 2007; 20(4):378–384. [PubMed: 17386343]

150. Benetos A, Thomas F, Joly L, Blacher J, Pannier B, Labat C, Salvi P, Smulyan H, Safar ME. Pulse Pressure Amplification A Mechanical Biomarker of Cardiovascular Risk. J Am Coll Cardiol. 2010; 55(10):1032–1037. [PubMed: 20202520]

151. Benetos A, Gautier S, Labat C, Salvi P, Valbusa F, Marino F, Toulza O, Agnoletti D, Zamboni M, Dubail D, Manckoundia P, Rolland Y, Hanon O, Perret-Guillaume C, Lacolley P, Safar ME, Guillemin F. Mortality and cardiovascular events are best predicted by low central/peripheral pulse pressure amplification but not by high blood pressure levels in elderly nursing home subjects: the PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study. J Am Coll Cardiol. 2012; 60(16):1503–1511. [PubMed: 22999729]

152. Kelly RP, Gibbs HH, O'Rourke MF, Daley JE, Mang K, Morgan JJ, Avolio AP. Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. Eur Heart J. 1990; 11(2):138–144. [PubMed: 2107077]

153. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension. 2009; 54(2):375–383. [PubMed: 19564542]

154. Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O'Rourke MF. Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform. J Clin Hypertens (Greenwich). 2008; 10(4):295–303. [PubMed: 18401227]

155. Westerhof N, Sipkema P, van den Bos GC, Elzinga G. Forward and backward waves in the arterial system. Cardiovasc Res. 1972; 6(6):648–656. [PubMed: 4656472]

156. Kobayashi S, Yano M, Kohno M, Obayashi M, Hisamatsu Y, Ryoke T, Ohkusa T, Yamakawa K, Matsuzaki M. Influence of aortic impedance on the development of pressure-overload left ventricular hypertrophy in rats. Circulation. 1996; 94(12):3362–3368. [PubMed: 8989152]

157. Hashimoto J, Westerhof BE, Westerhof N, Imai Y, O'Rourke MF. Different role of wave reflection magnitude and timing on left ventricular mass reduction during antihypertensive treatment. J Hypertens. 2008; 26(5):1017–1024. [PubMed: 18398345]

158. Fujimoto N, Onishi K, Tanabe M, Dohi K, Funabiki K, Kurita T, Yamanaka T, Nakajima K, Ito M, Nobori T, Nakano T. Nitroglycerin improves left ventricular relaxation by changing systolic loading sequence in patients with excessive arterial load. J Cardiovasc Pharmacol. 2005; 45(3): 211–216. [PubMed: 15725945]

159. Weber T, O'Rourke MF, Ammer M, Kvas E, Punzengruber C, Eber B. Arterial stiffness and arterial wave reflections are associated with systolic and diastolic function in patients with normal ejection fraction. Am J Hypertens. 2008; 21(11):1194–1202. [PubMed: 18787521]

160. Gillebert TC, Lew WY. Influence of systolic pressure profile on rate of left ventricular pressure fall. Am J Physiol. 1991; 261(3 Pt 2):H805–H813. [PubMed: 1887926]

161. Borlaug BA, Melenovsky V, Redfield MM, Kessler K, Chang HJ, Abraham TP, Kass DA. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. J Am Coll Cardiol. 2007; 50(16):1570–1577. [PubMed: 17936156]

162. Hori M, Inoue M, Kitakaze M, Kitabatake A, Abe H. Altered loading sequence as an underlying mechanism of afterload dependency of ventricular relaxation in hearts in situ. Jpn Circ J. 1985; 49(2):245–254. [PubMed: 3974130]

163. Shah SJ, Wasserstrom JA. Increased arterial wave reflection magnitude: a novel form of stage B heart failure? J Am Coll Cardiol. 2012; 60(21):2178–2181. [PubMed: 23103043]

164. Canepa M, Alghatrif M, Strait JB, Cheng HM, Chuang SY, Chen CH, Brunelli C, Ferrucci L, Lakatta EG. Early contribution of arterial wave reflection to left ventricular relaxation abnormalities in a community-dwelling population of normotensive and untreated hypertensive men and women. J Hum Hypertens. 2014; 28(2):85–91. [PubMed: 24048294]

165. O'Rourke MF, Pauca AL. Augmentation of the aortic and central arterial pressure waveform. Blood Press Monit. 2004; 9(4):179–185. [PubMed: 15311144]

166. Miyashita H. Clinical Assessment of Central Blood Pressure. Curr Hypertens Rev. 2012; 8(2):80–90. [PubMed: 22866025]

167. Manisty CH, Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. Br J Clin Pharmacol. 2013; 75(1):79–92. [PubMed: 22625662]

168. Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Perez G, Mendez AJ. Relation between ascending aortic pressures and outcomes in patients with angiographically demonstrated coronary artery disease. Am J Cardiol. 2005; 96(5):645–648. [PubMed: 16125487]

169. Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, Perez G, Mendez AJ. Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. Hypertension. 2005; 45(5):980–985. [PubMed: 15837821]

170. Redgrave J, Rabinowe S, Hollenberg NK, Williams GH. Correction of abnormal renal blood flow response to angiotensin II by converting enzyme inhibition in essential hypertensives. J Clin Invest. 1985; 75:1285–1290. [PubMed: 2985655]

171. Nelson MR, Stepanek J, Cevette M, Covalciuc M, Hurst RT, Tajik AJ. Noninvasive measurement of central vascular pressures with arterial tonometry: clinical revival of the pulse pressure waveform? Mayo Clin Proc. 2010; 85(5):460–472. [PubMed: 20435839]

172. Nunan D, Wassertheurer S, Lasserson D, Hametner B, Fleming S, Ward A, Heneghan C. Assessment of central haemomodynamics from a brachial cuff in a community setting. BMC Cardiovasc Disord. 2012; 12:48. [PubMed: 22734820]

173. Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: relationship to pressure wave forms. Circulation. 1980; 62(1):105–116. [PubMed: 7379273]

174. Segers, P.; Verdonck, P. Panvascular Medicine: Integrated clinical management. In: Lanzer, P.; Topol, E., editors. Principles of vascular physiology. New York: Springer; 2002.

175. Nichols WW, Edwards DG. Arterial elastance and wave reflection augmentation of systolic blood pressure: deleterious effects and implications for therapy. J Cardiovasc Pharmacol Ther. 2001; 6(1):5–21. [PubMed: 11452332]

176. Segers P, De BJ, Devos D, Rabben SI, Gillebert TC, Van Bortel LM, De SJ, De PA, Verdonck PR. Aortic reflection coefficients and their association with global indexes of wave reflection in healthy controls and patients with Marfan's syndrome. Am J Physiol Heart Circ Physiol. 2006; 290(6):H2385–H2392. [PubMed: 16399860]

177. O'Rourke MF. Time domain analysis of the arterial pulse in clinical medicine. Med Biol Eng Comput. 2009; 47(2):119–129. [PubMed: 18626676]

178. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol. 1983; 245(5 Pt 1):H773–H780. [PubMed: 6638199]

179. Segers P, Stergiopulos N, Westerhof N. Relation of effective arterial elastance to arterial system properties. Am J Physiol Heart Circ Physiol. 2002; 282(3):H1041–H1046. [PubMed: 11834502]

180. Chemla D, Antony I, Lecarpentier Y, Nitenberg A. Contribution of systemic vascular resistance and total arterial compliance to effective arterial elastance in humans. Am J Physiol Heart Circ Physiol. 2003; 285(2):H614–H620. [PubMed: 12689857]

181. Protogerou AD, Stergiou GS, Vlachopoulos C, Blacher J, Achimastos A. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: Evidence for specific class-effects of antihypertensive drugs on pressure amplification. Curr Pharm Des. 2009; 15(3):272–289. [PubMed: 19149618]

182. Protogerou AD, Papaioannou TG, Lekakis JP, Blacher J, Safar ME. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part I: (Patho)-physiology, rationale and perspective on pulse pressure amplification. Curr Pharm Des. 2009; 15(3):267–271. [PubMed: 19149617]

183. Mackenzie IS, McEniery CM, Dhakam Z, Brown MJ, Cockcroft JR, Wilkinson IB. Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension. Hypertension. 2009; 54(2):409–413. [PubMed: 19487582]

184. Mancia G, Grassi G. Joint National Committee VII and European Society of Hypertension/ European Society of Cardiology guidelines for evaluating and treating hypertension: a two-way road? J Am Soc Nephrol. 2005; 16 (Suppl 1):S74–S77. [PubMed: 15938040]

185. Kithas PA, Supiano MA. Spironolactone and hydrochlorothiazide decrease vascular stiffness and blood pressure in geriatric hypertension. J Am Geriatr Soc. 2010; 58(7):1327–1332. [PubMed: 20533969]

186. Boesby L, Elung-Jensen T, Strandgaard S, Kamper AL. Eplerenone attenuates pulse wave reflection in chronic kidney disease stage 3–4--a randomized controlled study. PLoS ONE. 2013; 8(5):e64549. [PubMed: 23704994]

187. Farquharson CA, Struthers AD. Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. Circulation. 2000; 101(6):594–597. [PubMed: 10673249]

188. Tsoucaris D, Benetos A, Legrand M, London GM, Safar ME. Proximal and distal pulse pressure after acute antihypertensive vasodilating drugs in Wistar-Kyoto and spontaneously hypertensive rats. J Hypertens. 1995; 13(2):243–249. [PubMed: 7615955]

189. Stokes GS, Barin ES, Gilfillan KL. Effects of isosorbide mononitrate and AII inhibition on pulse wave reflection in hypertension. Hypertension. 2003; 41(2):297–301. [PubMed: 12574098]

190. Pauca AL, Kon ND, O'Rourke MF. Benefit of glyceryl trinitrate on arterial stiffness is directly due to effects on peripheral arteries. Heart. 2005; 91(11):1428–1432. [PubMed: 15761047]

191. Cecelja M, Jiang B, Spector TD, Chowienczyk P. Progression of central pulse pressure over 1 decade of aging and its reversal by nitroglycerin a twin study. J Am Coll Cardiol. 2012; 59(5): 475–483. [PubMed: 22281250]

192. Van Bortel LM, Struijker-Boudier HA, Safar ME. Pulse pressure, arterial stiffness, and drug treatment of hypertension. Hypertension. 2001; 38(4):914–921. [PubMed: 11641309]

193. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, Thomas F, Pannier B, Asmar R, Zureik M, Safar M, Guize L. Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. Circulation. 2002; 105(10):1202–1207. [PubMed: 11889014]

194. Ait-Oufella H, Collin C, Bozec E, Laloux B, Ong KT, Dufouil C, Boutouyrie P, Laurent S. Long-term reduction in aortic stiffness: a 5. 3-year follow-up in routine clinical practice. J Hypertens. 2010; 28(11):2336–2341. [PubMed: 20683338]

195. Shahin Y, Khan JA, Chetter I. Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: a meta-analysis and meta-regression of randomised controlled trials. Atherosclerosis. 2012; 221(1):18–33. [PubMed: 22209214]

196. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation. 2006; 113(9):1213–1225. [PubMed: 16476843]

197. Edwards DG, Schofield RS, Magyari PM, Nichols WW, Braith RW. Effect of exercise training on central aortic pressure wave reflection in coronary artery disease. Am J Hypertens. 2004; 17(6):540–543. [PubMed: 15177529]

198. Edwards DG, Lang JT. Augmentation index and systolic load are lower in competitive endurance athletes. Am J Hypertens. 2005; 18(5 Pt 1):679–683. [PubMed: 15882551]

199. Pase MP, Grima NA, Sarris J. The effects of dietary and nutrient interventions on arterial stiffness: a systematic review. Am J Clin Nutr. 2011; 93(2):446–454. [PubMed: 21147858]

200. Dengo AL, Dennis EA, Orr JS, Marinik EL, Ehrlich E, Davy BM, Davy KP. Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. Hypertension. 2010; 55(4):855–861. [PubMed: 20212267]

201. Pal S, Radavelli-Bagatini S, Ho S. Potential benefits of exercise on blood pressure and vascular function. J Am Soc Hypertens. 2013; 7(6):494–506. [PubMed: 23992766]

202. Oliveira NL, Ribeiro F, Alves AJ, Campos L, Oliveira J. The effects of exercise training on arterial stiffness in coronary artery disease patients: a state-of-the-art review. Clin Physiol Funct Imaging. 2013

203. Sanchez-Gonzalez MA, Wong A, Vicil F, Gil R, Park SY, Figueroa A. Impact of passive vibration on pressure pulse wave characteristics. J Hum Hypertens. 2012; 26(10):610–615. [PubMed: 21697894]

204. Nichols WW, Estrada JC, Braith RW, Owens K, Conti CR. Enhanced external counterpulsation treatment improves arterial wall properties and wave reflection characteristics in patients with refractory angina. J Am Coll Cardiol. 2006; 48(6):1208–1214. [PubMed: 16979007]

205. KROEKER EJ, WOOD EH. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. Circ Res. 1955; 3(6):623–632. [PubMed: 13270378]

206. Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, Yin FC, Lakatta EG. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation. 1993; 88(4 Pt 1):1456–1462. [PubMed: 8403292]

207. Casey DP, Nichols WW, Braith RW. Impact of aging on central pressure wave reflection characteristics during exercise. Am J Hypertens. 2008; 21(4):419–424. [PubMed: 18246057]

208. Laurent P, Marenco P, Castagna O, Smulyan H, Blacher J, Safar ME. Differences in central systolic blood pressure and aortic stiffness between aerobically trained and sedentary individuals. J Am Soc Hypertens. 2011; 5(2):85–93. [PubMed: 21414563]

209. Heffernan KS, Jae SY, Tomayko E, Ishaque MR, Fernhall B, Wilund KR. Influence of arterial wave reflection on carotid blood pressure and intima-media thickness in older endurance trained men and women with pre-hypertension. Clin Physiol Funct Imaging. 2009; 29(3):193–200. [PubMed: 19236433]

210. Tabara Y, Yuasa T, Oshiumi A, Kobayashi T, Miyawaki Y, Miki T, Kohara K. Effect of acute and long-term aerobic exercise on arterial stiffness in the elderly. Hypertens Res. 2007; 30(10): 895–902. [PubMed: 18049020]

211. Seals DR, Tanaka H, Clevenger CM, Monahan KD, Reiling MJ, Hiatt WR, Davy KP, DeSouza CA. Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. J Am Coll Cardiol. 2001; 38(2):506–513. [PubMed: 11499745]

212. Heffernan KS, Fahs CA, Iwamoto GA, Jae SY, Wilund KR, Woods JA, Fernhall B. Resistance exercise training reduces central blood pressure and improves microvascular function in African American and white men. Atherosclerosis. 2009; 207(1):220–226. [PubMed: 19410255]

213. Otsuki T, Maeda S, Sugawara J, Kesen Y, Murakami H, Tanabe T, Miyauchi T, Kuno S, Ajisaka R, Matsuda M. Age-related reduction of systemic arterial compliance relates to decreased aerobic capacity during sub-maximal exercise. Hypertens Res. 2006; 29(10):759–765. [PubMed: 17283862]

214. Klonizakis M, Alkhatib A, Middleton G, Smith MF. Mediterranean diet- and exercise-induced improvement in age-dependent vascular activity. Clin Sci (Lond). 2013; 124(9):579–587. [PubMed: 23163793]

215. Sacre JW, Jennings GL, Kingwell BA. Exercise and dietary influences on arterial stiffness in cardiometabolic disease. Hypertension. 2014; 63(5):888–893. [PubMed: 24516111]

216. Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. Arteriosclerosis. 1986; 6(2):166–169. [PubMed: 3954670]

217. Oudegeest-Sander MH, Olde Rikkert MG, Smits P, Thijssen DH, van Dijk AP, Levine BD, Hopman MT. The effect of an advanced glycation end-product crosslink breaker and exercise training on vascular function in older individuals: a randomized factorial design trial. Exp Gerontol. 2013; 48(12):1509–1517. [PubMed: 24400341]

218. Edwards DG, Mastin CR, Kenefick RW. Wave reflection and central aortic pressure are increased in response to static and dynamic muscle contraction at comparable workloads. J Appl Physiol (1985). 2008; 104(2):439–445. [PubMed: 18079263]

219. Miyachi M. Effects of resistance training on arterial stiffness: a meta-analysis. Br J Sports Med. 2013; 47(6):393–396. [PubMed: 22267567]

220. Cortez-Cooper MY, DeVan AE, Anton MM, Farrar RP, Beckwith KA, Todd JS, Tanaka H. Effects of high intensity resistance training on arterial stiffness and wave reflection in women. Am J Hypertens. 2005; 18(7):930–934. [PubMed: 16053989]

221. Casey DP, Pierce GL, Howe KS, Mering MC, Braith RW. Effect of resistance training on arterial wave reflection and brachial artery reactivity in normotensive postmenopausal women. Eur J Appl Physiol. 2007; 100(4):403–408. [PubMed: 17394009]

222. Casey DP, Beck DT, Braith RW. Progressive resistance training without volume increases does not alter arterial stiffness and aortic wave reflection. Exp Biol Med (Maywood). 2007; 232(9): 1228–1235. [PubMed: 17895531]

223. Croymans DM, Krell SL, Oh CS, Katiraie M, Lam CY, Harris RA, Roberts CK. Effects of resistance training on central blood pressure in obese young men. J Hum Hypertens. 2014; 28(3): 157–164. [PubMed: 24005959]

224. Heffernan KS, Yoon ES, Sharman JE, Davies JE, Shih YT, Chen CH, Fernhall B, Jae SY. Resistance exercise training reduces arterial reservoir pressure in older adults with prehypertension and hypertension. Hypertens Res. 2013; 36(5):422–427. [PubMed: 23235716]

225. Taaffe DR, Galvao DA, Sharman JE, Coombes JS. Reduced central blood pressure in older adults following progressive resistance training. J Hum Hypertens. 2007; 21(1):96–98. [PubMed: 17096007]

226. Dwyer T, Sun C, Magnussen CG, Raitakari OT, Schork NJ, Venn A, Burns TL, Juonala M, Steinberger J, Sinaiko AR, Prineas RJ, Davis PH, Woo JG, Morrison JA, Daniels SR, Chen W, Srinivasan SR, Viikari JS, Berenson GS. Cohort Profile: the international childhood cardiovascular cohort (i3C) consortium. Int J Epidemiol. 2013; 42(1):86–96. [PubMed: 22434861]

227. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, Jacobson M, Mahoney L, Mietus-Snyder M, Rocchini A, Steinberger J, McCrindle B. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension. 2009; 54(5):919–950. [PubMed: 19729599]

228. Li S, Chen W, Srinivasan SR, Berenson GS. Childhood blood pressure as a predictor of arterial stiffness in young adults: the bogalusa heart study. Hypertension. 2004; 43(3):541–546. [PubMed: 14744922]

229. Koivistoinen T, Hutri-Kahonen N, Juonala M, Aatola H, Koobi T, Lehtimaki T, Viikari JS, Raitakari OT, Kahonen M. Metabolic syndrome in childhood and increased arterial stiffness in adulthood: the Cardiovascular Risk In Young Finns Study. Ann Med. 2011; 43(4):312–319. [PubMed: 21284533]

230. Aatola H, Koivistoinen T, Hutri-Kahonen N, Juonala M, Mikkila V, Lehtimaki T, Viikari JS, Raitakari OT, Kahonen M. Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation. 2010; 122(24):2521–2528. [PubMed: 21126970]

231. Mzayek F, Sherwin R, Hughes J, Hassig S, Srinivasan S, Chen W, Berenson GS. The association of birth weight with arterial stiffness at mid-adulthood: the Bogalusa Heart Study. J Epidemiol Community Health. 2009; 63(9):729–733. [PubMed: 19429574]

232. Miles KL, McDonnell BJ, Maki-Petaja KM, Yasmin, Cockcroft JR, Wilkinson IB, McEniery CM. The impact of birth weight on blood pressure and arterial stiffness in later life: the Enigma Study. J Hypertens. 2011; 29(12):2324–2331. [PubMed: 22025237]

233. Ahimastos AA, Formosa M, Dart AM, Kingwell BA. Gender differences in large artery stiffness pre- and post puberty. J Clin Endocrinol Metab. 2003; 88(11):5375–5380. [PubMed: 14602776]

234. Niboshi A, Hamaoka K, Sakata K, Inoue F. Characteristics of brachial-ankle pulse wave velocity in Japanese children. Eur J Pediatr. 2006; 165(9):625–629. [PubMed: 16636815]

235. Riggio S, Mandraffino G, Sardo MA, Iudicello R, Camarda N, Imbalzano E, Alibrandi A, Saitta C, Carerj S, Arrigo T, Saitta A. Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children. Eur J Clin Invest. 2010; 40(3):250–257. [PubMed: 20415700]

236. Urbina EM, Khoury PR, McCoy CE, Dolan LM, Daniels SR, Kimball TR. Triglyceride to HDL-C ratio and increased arterial stiffness in children, adolescents, and young adults. Pediatrics. 2013; 131(4):e1082–e1090. [PubMed: 23460684]

237. Kyvelou SM, Vyssoulis GP, Karpanou EA, Adamopoulos DN, Gialernios TP, Spanos PG, Cokkinos DV, Stefanadis CI. Arterial hypertension parental burden affects arterial stiffness and wave reflection to the aorta in young offsprings. Int J Cardiol. 2010; 144(1):156–160. [PubMed: 19174311]

238. Kucerova J, Filipovsky J, Staessen JA, Cwynar M, Wojciechowska W, Stolarz K, Kuznetsova T, Gasowski J, Dolejsova M, Grodzicki T, Kawecka-Jaszcz K, Fagard R. Arterial characteristics in normotensive offspring of parents with or without a history of hypertension. Am J Hypertens. 2006; 19(3):264–269. [PubMed: 16500511]

239. Lurbe E, Torro I, Garcia-Vicent C, Alvarez J, Fernandez-Fornoso JA, Redon J. Blood pressure and obesity exert independent influences on pulse wave velocity in youth. Hypertension. 2012; 60(2):550–555. [PubMed: 22733475]

240. Urbina EM, Khoury PR, McCoy C, Daniels SR, Kimball TR, Dolan LM. Cardiac and vascular consequences of pre-hypertension in youth. J Clin Hypertens (Greenwich). 2011; 13(5):332–342. [PubMed: 21545394]

241. Zhu H, Yan W, Ge D, Treiber FA, Harshfield GA, Kapuku G, Snieder H, Dong Y. Cardiovascular characteristics in American youth with prehypertension. Am J Hypertens. 2007; 20(10):1051–1057. [PubMed: 17903687]

242. Dietz LJ, Matthews KA. Depressive symptoms and subclinical markers of cardiovascular disease in adolescents. J Adolesc Health. 2011; 48(6):579–584. [PubMed: 21575817]

243. Midei AJ, Matthews KA. Social relationships and negative emotional traits are associated with central adiposity and arterial stiffness in healthy adolescents. Health Psychol. 2009; 28(3):347–353. [PubMed: 19450041]

244. Thurston RC, Matthews KA. Racial and socioeconomic disparities in arterial stiffness and intima media thickness among adolescents. Soc Sci Med. 2009; 68(5):807–813. [PubMed: 19147264]

245. van de Laar RJ, Stehouwer CD, Boreham CA, Murray LM, Schalkwijk CG, Prins MH, Twisk JW, Ferreira I. Continuing smoking between adolescence and young adulthood is associated with higher arterial stiffness in young adults: the Northern Ireland Young Hearts Project. J Hypertens. 2011; 29(11):2201–2209. [PubMed: 21897293]

246. Sakuragi S, Abhayaratna K, Gravenmaker KJ, O'Reilly C, Srikusalanukul W, Budge MM, Telford RD, Abhayaratna WP. Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. Hypertension. 2009; 53(4):611–616. [PubMed: 19273744]

247. Otsuki T, Maeda S, Iemitsu M, Saito Y, Tanimura Y, Ajisaka R, Miyauchi T. Relationship between arterial stiffness and athletic training programs in young adult men. Am J Hypertens. 2007; 20(9):967–973. [PubMed: 17765138]

248. Chen Y, Dangardt F, Osika W, Berggren K, Gronowitz E, Friberg P. Age- and sex-related differences in vascular function and vascular response to mental stress. Longitudinal and cross-sectional studies in a cohort of healthy children and adolescents. Atherosclerosis. 2012; 220(1): 269–274. [PubMed: 22078247]

249. Edwards NM, Daniels SR, Claytor RP, Khoury PR, Dolan LM, Kimball TR, Urbina EM. Physical activity is independently associated with multiple measures of arterial stiffness in adolescents and young adults. Metabolism. 2012; 61(6):869–872. [PubMed: 22153839]

250. Arnberg K, Larnkjaer A, Michaelsen KF, Molgaard C. Central adiposity and protein intake are associated with arterial stiffness in overweight children. J Nutr. 2012; 142(5):878–885. [PubMed: 22437560]

251. Zhu H, Yan W, Tan Y, Li K, Kapuku G, Treiber FA, Su S, Harshfield GA, Snieder H, Dong Y. Adhesion molecule polymorphisms and pulse wave velocity in American youth. Twin Res Hum Genet. 2008; 11(5):517–523. [PubMed: 18828734]

252. Urbina EM, Kimball TR, Khoury PR, Daniels SR, Dolan LM. Increased arterial stiffness is found in adolescents with obesity or obesity-related type 2 diabetes mellitus. J Hypertens. 2010; 28(8): 1692–1698. [PubMed: 20647860]

253. Shah AS, Dolan LM, Gao Z, Kimball TR, Urbina EM. Clustering of risk factors: a simple method of detecting cardiovascular disease in youth. Pediatrics. 2011; 127(2):e312–e318. [PubMed: 21242216]

254. Lee JW, Lee DC, Im JA, Shim JY, Kim SM, Lee HR. Insulin resistance is associated with arterial stiffness independent of obesity in male adolescents. Hypertens Res. 2007; 30(1):5–11. [PubMed: 17460366]

255. Miyai N, Arita M, Miyashita K, Morioka I, Takeda S. The influence of obesity and metabolic risk variables on brachial-ankle pulse wave velocity in healthy adolescents. J Hum Hypertens. 2009; 23(7):444–450. [PubMed: 19078989]

256. Urbina EM, Gao Z, Khoury PR, Martin LJ, Dolan LM. Insulin resistance and arterial stiffness in healthy adolescents and young adults. Diabetologia. 2012; 55(3):625–631. [PubMed: 22193511]

257. Wadwa RP, Urbina EM, Anderson AM, Hamman RF, Dolan LM, Rodriguez BL, Daniels SR, Dabelea D. Measures of arterial stiffness in youth with type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. Diabetes Care. 2010; 33(4):881–886. [PubMed: 20067960]

258. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999; 99(18):2434–2439. [PubMed: 10318666]

259. Dursun I, Poyrazoglu HM, Gunduz Z, Ulger H, Yykylmaz A, Dusunsel R, Patyroglu T, Gurgoze M. The relationship between circulating endothelial microparticles and arterial stiffness and atherosclerosis in children with chronic kidney disease. Nephrol Dial Transplant. 2009; 24(8): 2511–2518. [PubMed: 19244228]

260. Covic A, Mardare N, Gusbeth-Tatomir P, Brumaru O, Gavrilovici C, Munteanu M, Prisada O, Goldsmith DJ. Increased arterial stiffness in children on haemodialysis. Nephrol Dial Transplant. 2006; 21(3):729–735. [PubMed: 16221688]

261. Aoun B, Lorton F, Wannous H, Levy B, Ulinski T. Aortic stiffness in ESRD children before and after renal transplantation. Pediatr Nephrol. 2010; 25(7):1331–1336. [PubMed: 20352455]

262. Briese S, Claus M, Querfeld U. Arterial stiffness in children after renal transplantation. Pediatr Nephrol. 2008; 23(12):2241–2245. [PubMed: 18584211]

263. Cseprekal O, Kis E, Schaffer P, Othmane TH, Fekete BC, Vannay A, Szabo AJ, Remport A, Szabo A, Tulassay T, Reusz GS. Pulse wave velocity in children following renal transplantation. Nephrol Dial Transplant. 2009; 24(1):309–315. [PubMed: 18775897]

264. Yu MC, Yu MS, Yu MK, Lee F, Huang WH. Acute reversible changes of brachial-ankle pulse wave velocity in children with acute poststreptococcal glomerulonephritis. Pediatr Nephrol. 2011; 26(2):233–239. [PubMed: 20640906]

265. Charakida M, Loukogeorgakis SP, Okorie MI, Masi S, Halcox JP, Deanfield JE, Klein NJ. Increased arterial stiffness in HIV-infected children: risk factors and antiretroviral therapy. Antivir Ther. 2009; 14(8):1075–1079. [PubMed: 20032537]

266. Cheung YF, Brogan PA, Pilla CB, Dillon MJ, Redington AN. Arterial distensibility in children and teenagers: normal evolution and the effect of childhood vasculitis. Arch Dis Child. 2002; 87(4):348–351. [PubMed: 12244018]

267. Cheung YF, Yung TC, Tam SC, Ho MH, Chau AK. Novel and traditional cardiovascular risk factors in children after Kawasaki disease: implications for premature atherosclerosis. J Am Coll Cardiol. 2004; 43(1):120–124. [PubMed: 14715193]

268. Klinge A, Allen J, Murray A, O'Sullivan J. Increased pulse wave velocity and blood pressure in children who have undergone cardiac transplantation. J Heart Lung Transplant. 2009; 28(1):21–25. [PubMed: 19134526]

269. Cheung YF, Ou X, Wong SJ. Central and peripheral arterial stiffness in patients after surgical repair of tetralogy of Fallot: implications for aortic root dilatation. Heart. 2006; 92(12):1827–1830. [PubMed: 16775086]

270. Saiki H, Kojima T, Seki M, Masutani S, Senzaki H. Marked disparity in mechanical wall properties between ascending and descending aorta in patients with tetralogy of Fallot. Eur J Cardiothorac Surg. 2012; 41(3):570–573. [PubMed: 22345178]

271. Seki M, Kurishima C, Kawasaki H, Masutani S, Senzaki H. Aortic stiffness and aortic dilation in infants and children with tetralogy of Fallot before corrective surgery: evidence for intrinsically abnormal aortic mechanical property. Eur J Cardiothorac Surg. 2012; 41(2):277–282. [PubMed: 21683611]

272. Grotenhuis HB, Ottenkamp J, Fontein D, Vliegen HW, Westenberg JJ, Kroft LJ, de RA. Aortic elasticity and left ventricular function after arterial switch operation: MR imaging--initial experience. Radiology. 2008; 249(3):801–809. [PubMed: 18941160]

273. de DM, Pilla C, Kattenhorn M, Donald A, Zadinello M, Wallace S, Redington A, Deanfield J. Ambulatory blood pressure, left ventricular mass, and conduit artery function late after successful repair of coarctation of the aorta. J Am Coll Cardiol. 2003; 41(12):2259–2265. [PubMed: 12821257]

274. Kenny D, Polson JW, Martin RP, Caputo M, Wilson DG, Cockcroft JR, Paton JF, Wolf AR. Relationship of aortic pulse wave velocity and baroreceptor reflex sensitivity to blood pressure control in patients with repaired coarctation of the aorta. Am Heart J. 2011; 162(2):398–404. [PubMed: 21835303]

275. Ou P, Celermajer DS, Raisky O, Jolivet O, Buyens F, Herment A, Sidi D, Bonnet D, Mousseaux E. Angular (Gothic) aortic arch leads to enhanced systolic wave reflection, central aortic stiffness, and increased left ventricular mass late after aortic coarctation repair: evaluation with

magnetic resonance flow mapping. J Thorac Cardiovasc Surg. 2008; 135(1):62–68. [PubMed: 18179920]

276. Ou P, Celermajer DS, Jolivet O, Buyens F, Herment A, Sidi D, Bonnet D, Mousseaux E. Increased central aortic stiffness and left ventricular mass in normotensive young subjects after successful coarctation repair. Am Heart J. 2008; 155(1):187–193. [PubMed: 18082512]
277. Sarkola T, Redington AN, Slorach C, Hui W, Bradley T, Jaeggi E. Assessment of vascular phenotype using a novel very-high-resolution ultrasound technique in adolescents after aortic coarctation repair and/or stent implantation: relationship to central haemodynamics and left ventricular mass. Heart. 2011; 97(21):1788–1793. [PubMed: 21795301]
278. Payne RA, Hilling-Smith RC, Webb DJ, Maxwell SR, Denvir MA. Augmentation index assessed by applanation tonometry is elevated in Marfan Syndrome. J Cardiothorac Surg. 2007; 2:43. [PubMed: 17956619]
279. Tedesco MA, Di SG, Ratti G, Natale F, Calabrese E, Grassia C, Iacono A, Lama G. Arterial distensibility and ambulatory blood pressure monitoring in young patients with neurofibromatosis type 1. Am J Hypertens. 2001; 14(6 Pt 1):559–566. [PubMed: 11411736]
280. Salvi P, Revera M, Joly L, Reusz G, Iaia M, Benkhedda S, Chibane A, Parati G, Benetos A, Temmar M. Role of birth weight and postnatal growth on pulse wave velocity in teenagers. J Adolesc Health. 2012; 51(4):373–379. [PubMed: 22999838]
281. Fischer DC, Schreiver C, Heimhalt M, Noerenberg A, Haffner D. Pediatric reference values of carotid-femoral pulse wave velocity determined with an oscillometric device. J Hypertens. 2012; 30(11):2159–2167. [PubMed: 22940681]
282. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation. 1985; 71(2):202–210. [PubMed: 3965165]
283. Gardner AW, Parker DE. Association between arterial compliance and age in participants 9 to 77 years old. Angiology. 2010; 61(1):37–41. [PubMed: 19638351]
284. Voges I, Jerosch-Herold M, Hedderich J, Pardun E, Hart C, Gabbert DD, Hansen JH, Petko C, Kramer HH, Rickers C. Normal values of aortic dimensions, distensibility, and pulse wave velocity in children and young adults: a cross-sectional study. J Cardiovasc Magn Reson. 2012; 14:77. [PubMed: 23151055]
285. Senzaki H, Akagi M, Hishi T, Ishizawa A, Yanagisawa M, Masutani S, Kobayashi T, Awa S. Age-associated changes in arterial elastic properties in children. Eur J Pediatr. 2002; 161(10): 547–551. [PubMed: 12297902]
286. Choi CU, Kim EJ, Kim SH, Shin SY, Choi UJ, Kim JW, Lim HE, Rha SW, Park CG, Seo HS, Oh DJ. Differing effects of aging on central and peripheral blood pressures and pulse wave velocity: a direct intraarterial study. J Hypertens. 2010; 28(6):1252–1260. [PubMed: 20453666]
287. Latham RD, Westerhof N, Sipkema P, Rubal BJ, Reuderink P, Murgo JP. Regional wave travel and reflections along the human aorta: a study with six simultaneous micromanometric pressures. Circulation. 1985; 72(6):1257–1269. [PubMed: 4064270]
288. Choi CU, Park EB, Suh SY, Kim JW, Kim EJ, Rha SW, Seo HS, Oh DJ, Park CG. Impact of aortic stiffness on cardiovascular disease in patients with chest pain: assessment with direct intra-arterial measurement. Am J Hypertens. 2007; 20(11):1163–1169. [PubMed: 17954362]
289. Lim HE, Park CG, Shin SH, Ahn JC, Seo HS, Oh DJ. Aortic pulse wave velocity as an independent marker of coronary artery disease. Blood Press. 2004; 13(6):369–375. [PubMed: 15771222]
290. Kilic H, Yelgec S, Salih O, Akdemir R, Karakurt O, Cagirci G, Yeter E, Acikel S, Dogan M, Arslantas U, Baha RM. An invasive but simple and accurate method for ascending aorta-femoral artery pulse wave velocity measurement. Blood Press. 2013; 22(1):45–50. [PubMed: 22747433]
291. Podolec P, Kopec G, Podolec J, Wilkolek P, Krochin M, Rubis P, Cwynar M, Grodzicki T, Zmudka K, Tracz W. Aortic pulse wave velocity and carotid-femoral pulse wave velocity: similarities and discrepancies. Hypertens Res. 2007; 30(12):1151–1158. [PubMed: 18344619]

292. Hickson SS, Butlin M, Graves M, Taviani V, Avolio AP, McEniery CM, Wilkinson IB. The relationship of age with regional aortic stiffness and diameter. JACC Cardiovasc Imaging. 2010; 3(12):1247–1255. [PubMed: 21163453]

293. Westenberg JJ, van Poelgeest EP, Steendijk P, Grotenhuis HB, Jukema JW, de RA. Bramwell-Hill modeling for local aortic pulse wave velocity estimation: a validation study with velocity-encoded cardiovascular magnetic resonance and invasive pressure assessment. J Cardiovasc Magn Reson. 2012; 14:2. [PubMed: 22230116]

294. Wilkinson IB, McEniery CM, Schillaci G, Boutouyrie P, Segers P, Donald A, Chowienczyk PJ. ARTERY Society guidelines for validation of non-invasive haemodynamic measurement devices: Part 1, arterial pulse wave velocity. Artery Research. 2010; 4:34–40.

295. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 1(8476):307–310. [PubMed: 2868172]

296. Segers PK, Trachet B, Swillens A, Vermeersch S, Mahieu D, Rietzschel E, de Buyzere M, Van Bortel L. Limitations and pitfalls of non-invasive measurement of arterial pressure wave reflections and pulse wave velocity. Artery Research. 2009; 3:79–88.

297. Sugawara J, Hayashi K, Yokoi T, Tanaka H. Age-associated elongation of the ascending aorta in adults. JACC Cardiovasc Imaging. 2008; 1(6):739–748. [PubMed: 19356510]

298. MCDONALD DA. Regional pulse-wave velocity in the arterial tree. J Appl Physiol. 1968; 24(1): 73–78. [PubMed: 5635773]

299. Paini A, Boutouyrie P, Calvet D, Tropeano AI, Laloux B, Laurent S. Carotid and aortic stiffness: determinants of discrepancies. Hypertension. 2006; 47(3):371–376. [PubMed: 16446398]

300. Weber T, Hametner B, Wassertheurer S. Travel distance estimation for carotid femoral pulse wave velocity: is the gold standard a real one ? J Hypertens. 2011; 29(12):2491–2493. [PubMed: 22075956]

301. Huybrechts SA, Devos DG, Vermeersch SJ, Mahieu D, Achten E, De Backer TL, Segers P, Van Bortel LM. Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path lengths determined by MRI and superficial measurements. J Hypertens. 2011; 29(8):1577–1582. [PubMed: 21666491]

302. Joly L, Perret-Guillaume C, Kearney-Schwartz A, Salvi P, Mandry D, Marie PY, Karcher G, Rossignol P, Zannad F, Benetos A. Pulse wave velocity assessment by external noninvasive devices and phase-contrast magnetic resonance imaging in the obese. Hypertension. 2009; 54(2): 421–426. [PubMed: 19506096]

303. Bossuyt J, Van DV, Azermai M, Vermeersch SJ, De Backer TL, Devos DG, Heyse C, Filipovsky J, Segers P, Van Bortel LM. Noninvasive assessment of carotid-femoral pulse wave velocity: the influence of body side and body contours. J Hypertens. 2013; 31(5):946–951. [PubMed: 23511340]

304. Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. J Hypertens. 2009; 27(10):2022–2027. [PubMed: 19550355]

305. Horvath IG, Nemeth A, Lenkey Z, Alessandri N, Tufano F, Kis P, Gaszner B, Cziraki A. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. J Hypertens. 2010; 28(10):2068–2075. [PubMed: 20651604]

306. Baumann M, Wassertheurer S, Suttmann Y, Burkhardt K, Heemann U. Aortic pulse wave velocity predicts mortality in chronic kidney disease stages 2–4. J Hypertens. 2014; 32(4):899–903. [PubMed: 24609217]

307. Stewart AD, Millasseau SC, Kearney MT, Ritter JM, Chowienczyk PJ. Effects of inhibition of basal nitric oxide synthesis on carotid-femoral pulse wave velocity and augmentation index in humans. Hypertension. 2003; 42(5):915–918. [PubMed: 12975386]

308. Giannattasio C, Failla M, Mangoni AA, Scandola L, Fraschini N, Mancia G. Evaluation of arterial compliance in humans. Clin Exp Hypertens. 1996; 18(3–4):347–362. [PubMed: 8743026]

309. Giannattasio C, Vincenti A, Failla M, Capra A, Ciro A, De CS, Gentile G, Brambilla R, Mancia G. Effects of heart rate changes on arterial distensibility in humans. Hypertension. 2003; 42(3): 253–256. [PubMed: 12913054]

310. Haesler E, Lyon X, Pruvot E, Kappenberger L, Hayoz D. Confounding effects of heart rate on pulse wave velocity in paced patients with a low degree of atherosclerosis. J Hypertens. 2004; 22(7):1317–1322. [PubMed: 15201547]

311. Albaladejo P, Copie X, Boutouyrie P, Laloux B, Declere AD, Smulyan H, Benetos A. Heart rate, arterial stiffness, and wave reflections in paced patients. Hypertension. 2001; 38(4):949–952. [PubMed: 11641315]

312. Albaladejo P, Challande P, Kakou A, Benetos A, Labat C, Louis H, Safar ME, Lacolley P. Selective reduction of heart rate by ivabradine: effect on the visco-elastic arterial properties in rats. J Hypertens. 2004; 22(9):1739–1745. [PubMed: 15311102]

313. Stefanadis C, Dernellis J, Vavuranakis M, Tsiamis E, Vlachopoulos C, Toutouzas K, Diamandopoulos L, Pitsavos C, Toutouzas P. Effects of ventricular pacing-induced tachycardia on aortic mechanics in man. Cardiovasc Res. 1998; 39(2):506–514. [PubMed: 9798535]

314. Tan I, Butlin M, Liu YY, Ng K, Avolio AP. Heart rate dependence of aortic pulse wave velocity at different arterial pressures in rats. Hypertension. 2012; 60(2):528–533. [PubMed: 22585952]

315. Millasseau SC, Stewart AD, Patel SJ, Redwood SR, Chowienczyk PJ. Evaluation of carotid-femoral pulse wave velocity: influence of timing algorithm and heart rate. Hypertension. 2005; 45(2):222–226. [PubMed: 15642772]

316. Rajzer MW, Wojciechowska W, Klocek M, Palka I, Brzozowska-Kiszka M, Kawecka-Jaszcz K. Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph. J Hypertens. 2008; 26(10):2001–2007. [PubMed: 18806624]

317. Vermeersch SJ, Rietzschel ER, De Buyzere ML, Van Bortel LM, Gillebert TC, Verdonck PR, Laurent S, Segers P, Boutouyrie P. Distance measurements for the assessment of carotid to femoral pulse wave velocity. J Hypertens. 2009; 27(12):2377–2385. [PubMed: 19898251]

318. Ong KT, Delerme S, Pannier B, Safar ME, Benetos A, Laurent S, Boutouyrie P. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. J Hypertens. 2011; 29(6):1034–1042. [PubMed: 21519280]

319. Mallareddy M, Parikh CR, Peixoto AJ. Effect of angiotensin-converting enzyme inhibitors on arterial stiffness in hypertension: systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2006; 8(6):398–403. [PubMed: 16760677]

320. Wang M, Jiang L, Monticone RE, Lakatta EG. Proinflammation: the key to arterial aging. Trends Endocrinol Metab. 2013

321. Sola J, Proenca M, Chetelat O. Wearable PWV technologies to measure Blood Pressure: eliminating brachial cuffs. Conf Proc IEEE Eng Med Biol Soc. 2013; 2013:4098–4101. [PubMed: 24110633]

Table 1

Applying Classification of Recommendations and Level of Evidence

		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: Not Helpful; Treatment: No Proven benefit COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful; Treatment: Harmful to Patients
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	**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

	SIZE OF TREATMENT EFFECT				
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 considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit	COR III: Harm
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		is not recommended is not indicated should not be performed/administered/other is not useful/beneficial/effective	potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/other

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.

Table 2

[Section 6]: Recommendations for grading comparisons of devices/procedures for measuring PWV with a gold standard device

Excellent accuracy: mean difference ≤ 0.5 m/sec and SD ≤ 0.8 m/sec
Acceptable accuracy: mean difference < 1 m/sec and SD ≤ 1.5 m/sec
Poor accuracy: mean difference ≥ 1 m/sec or SD > 1.5 m/sec