

## STATE-OF-THE-ART PAPER

# Aortic Stiffness

## Current Understanding and Future Directions

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The aorta stiffens with aging, a process that is accelerated by arterial hypertension. Decreased arterial compliance is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall. The use of different imaging techniques optimized for assessment of vascular elasticity and quantification of luminal and vessel wall parameters allows for a comprehensive and detailed view of the vascular system. In addition, several studies have also documented the prognostic importance of arterial stiffness (AS) in various populations as an independent predictor of cardiovascular morbidity and all-cause mortality. Measurement of AS by applanation tonometry with pulse-wave velocity has been the gold-standard method and is well-validated in large populations as a strong predictor of adverse cardiovascular outcomes. Because aortic stiffness depends on the prevailing blood pressure, effective antihypertensive treatment is expected to reduce it in proportion to the blood pressure reduction. Nevertheless, drugs lowering blood pressure might differ in their effects on structure and function of the arterial walls. This review paper not only will discuss the current understanding and clinical significance of AS but also will review the effects of various pharmacological and nonpharmacological interventions that can be used to preserve the favorable profile of a more compliant and less stiff aorta.

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### Understanding the Concept of Aortic Stiffness

Arterial stiffness is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall. Degenerative stiffness of the arterial beds is referred as arteriosclerosis and it should be differentiated from atherosclerosis, which is defined as the occlusive result of endovascular inflammatory disease, lipid oxidation, and plaque formation. Both tend to coexist and refer to a progressive, diffuse, and age-related process that occurs in all vascular beds (1).

Vessel walls are 3-dimensional structures with complex vascular mechanics (2,3). For a better understanding of the concept of aortic stiffness (AS), it is important to highlight some key points:

1. Large arteries also have, aside from their properties of providing a conduit for blood to reach peripheral tissues, a critical role in providing adequate vascular buffering to each ventricular contraction through arterial-ventricular

coupling. As such, the histological structure of the aorta varies immensely according to its site and function as a reservoir and conductive system (Windkessel principle). For instance, the proximal aorta is rich in elastin that allows the support of each systolic impulse and accommodates the stroke volume. Thus, the thoracic aorta and its immediate branches show greater elasticity, whereas more distal vessels become progressively stiffer, given the predominance of collagen fibers (5,000 times the tensile modulus of elastin) (2).

2. Stress ( $\sigma$ ) is defined as the force applied/area to a particular object ( $\sigma = F/A$ ). It can be applied in any direction: at radial, circumferential, and longitudinal components. Circumferential wall stress, defined by Laplace's law, is directly proportional to the vessel pressure and radius and inversely proportional to its thickness. Strain ( $\epsilon$ ) is the resulting deformation (percentage change in length) of an object/material subjected to a stress force. It is dimensionless (no units) and is defined as:

$$\epsilon = L - L_0 / L_0$$

where L is the final length and  $L_0$  is the initial length.

3. The elastic modulus (E), also known as Young's modulus, is the stress/strain ratio. In most biologic materials, this relation is nonlinear, and the slope defines the

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## Abbreviations and Acronyms

**AD** = aortic distensibility

**AS** = aortic stiffness

**CFPWV** = carotid-femoral pulse-wave velocity

**CPAP** = continuous positive airway pressure

**CV** = cardiovascular

**FBN** = fibrillin

**LV** = left ventricular

**MRI** = magnetic resonance imaging

**PWV** = pulse wave velocity

**SBP** = systolic blood pressure

intrinsic elastic properties of the wall material.  $E$  is expressed by the formula:

$$E = \frac{\sigma}{C}$$

where  $C$  is the arterial compliance.

4. Stiffness should be understood as the resistance to deformation. Measures of arterial stiffness depend on 3 independent and interdependent variables of the particular vessel studied ( $E$ ,  $h$ , and  $r$ ). The Moens-Korteweg equation defines pulse-wave velocity (PWV), assuming that

there are no significant changes in the vessel area or wall thickness, as the following:

$$PWV = \sqrt{\frac{E_{inc} \cdot h}{2rp}}$$

where  $E_{inc}$  is the incremental elastic modulus of the vessel,  $h$  = vessel wall thickness,  $r$  = vessel radius, and  $\rho$  = density of blood. Units used are centimeters/second or meters/second. Note that PWV is proportional to the square root of vessel stiffness and not particularly sensitive to changes in vessel dimensions or thickness. Aortic stiffness is dependent on the complex interaction between the vascular smooth muscle cells with the extracellular matrix containing elastin, collagen, and fibrillin (FBN) fibers (3,4).

5. Arterial compliance ( $C$ ) is the absolute change in area (or change in diameter =  $\Delta D$ ) for a given pressure step ( $\Delta P$ ) at a fixed vessel length. It is the reciprocal of stiffness and is defined as:

$$C = \frac{\Delta D}{\Delta P}$$

Distensibility, by contrast, is defined as the relative compliance or relative change in diameter/area/pressure step increase. It is the inverse of the elastic modulus ( $E$ ).

6. The morphology of a pulse contour is that any point along the vascular tree represents the sum of the forward and reflected pressure waves at that point and depends on 3 factors: the amplitude and duration of left ventricular (LV) ejection, the amplitude of the reflected wave, and the velocity of the reflected wave from the periphery. The end-product—also known as augmentation index and often used as a surrogate of aortic stiffness—can be affected by several other factors, such as heart rate, LV

ejection fraction, and duration (5), losing its clinical utility particularly in diabetic persons (6) and individuals  $\geq 60$  years of age (7).

7. In the long term, pulsatility causes stretching of the load-bearing elastic lamellae and mechanical stress on the wall contributing to structural changes and stiffening (8) (Figs. 1 and 2). Over time, all these factors contribute to increased large-artery stiffness which worsens with aging (Fig. 3) (9).
8. Genetics seems to also play a role in the development of AS. Polymorphisms of the matrix metalloprotein-9 gene were independent predictors of increased aortic stiffness (10).

## How to Measure AS

PWV is the most validated method to noninvasively quantify arterial stiffness. It is considered the gold standard index of AS, given its simplicity, accuracy, reproducibility, and strong prediction of adverse outcomes (11–13). PWV can be determined by measuring the pulse transit time from the pressure waveforms at the 2 sites along a vascular segment. The distance ( $L$ ) is divided by the wave foot-to-foot time ( $\Delta T$ ) it takes for that forward wave to reach the end measuring point (PWV) (Fig. 4). Pulse wave velocity is inversely related to vascular compliance. Hence, a stiffer vessel will conduct the pulse wave faster than a more distensible and compliant vessel.

PWV is a regional functional measurement of arterial stiffness over a certain arterial length, whereas strain, compliance, and distensibility are local markers of arterial elasticity. Local AS has been characterized—to allow comparisons between indexes—as the inverse relation of aortic distensibility (AD) (13,14) as demonstrated by the Bramwell-Hill equation (15) and expressed in meters/second:

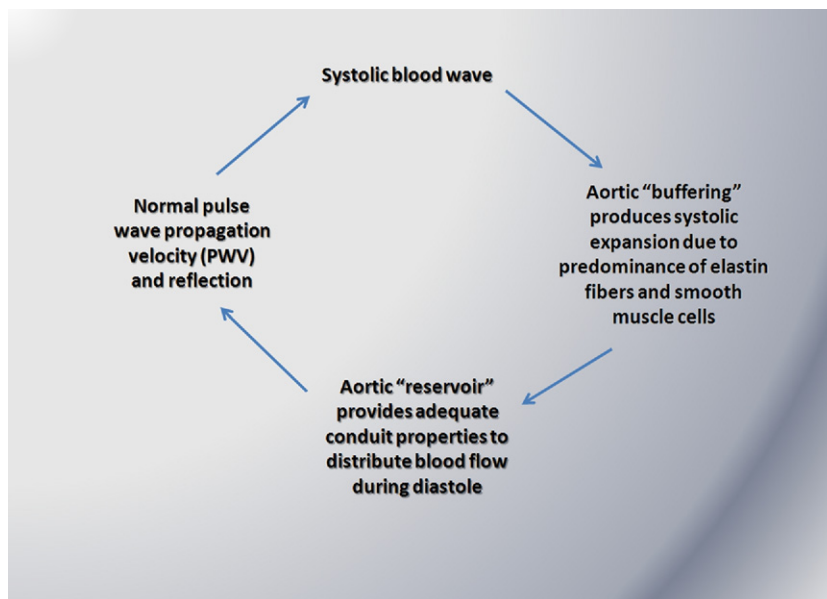
$$PWV \propto \frac{1}{\sqrt{\text{Distensibility}}} \text{ or } D = (3.57 / PWV)^2$$

Redheuil et al. (16) showed that local aortic elastic properties measured by magnetic resonance imaging (MRI) were markedly decreased before the fifth decade of life, whereas concomitant increase in aortic arch PWV (increased AS) was seen demonstrating that inverse relationship.

Other investigators (3,4) have proposed that aortic compliance and distensibility are the absolute and relative changes for pressure steps, respectively. Aortic distensibility is the relative cross-sectional diameter (or area) change for a given pressure step at fixed vessel length. The frequently used formula that expresses this relationship is:

$$\text{Aortic Distensibility} = \frac{A_{\text{max}} - A_{\text{min}}}{A_{\text{min}} \times \text{central pulse pressure}}$$

where  $A_{\text{max}}$  = maximal aortic lumen and  $A_{\text{min}}$  = minimal aortic lumen.

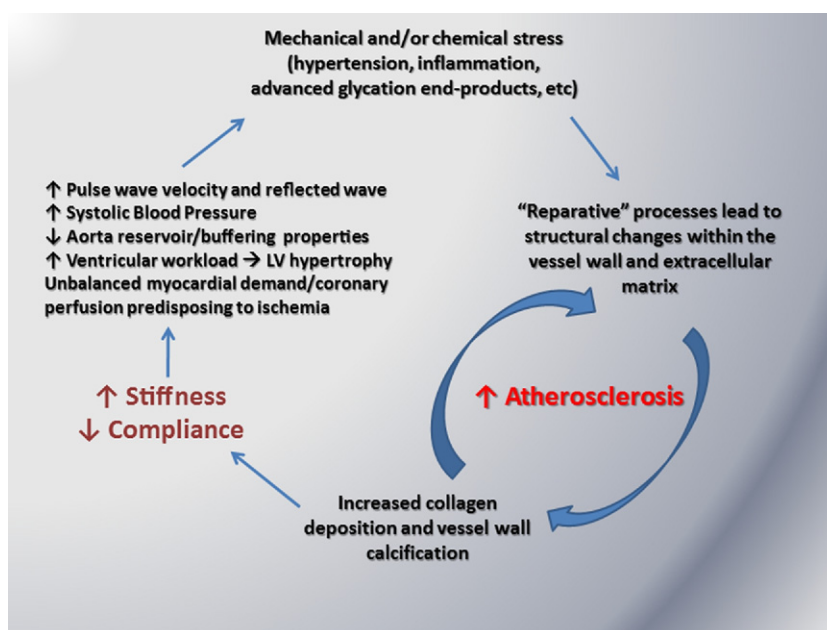


**Figure 1** Physiologic Properties of the Aorta as a Reservoir and Conduitive System: The Windkessel Principle

The aorta is regionally heterogeneous and not a simple conduit for blood distribution. The viscoelastic properties of the proximal aorta absorb the energy of left ventricular ejection and dampen pulsatile flow.

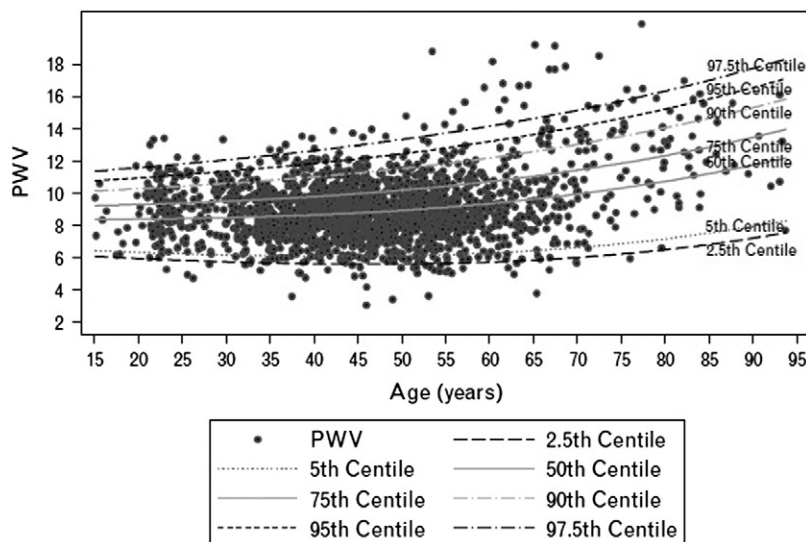
As with any quantification technique, care must be taken to consider the methodology being used when comparing results between patient groups and among different studies (Table 1).

**Measurement of AS by applanation tonometry and oscillometric method.** The applanation tonometry principle for arteries followed directly from the ocular application, given the propensity for a circular arterial segment to be



**Figure 2** Insights Leading to Structural Changes in the Aorta and its Functioning

Several processes can alter the homeostasis of aortic elastic properties leading to increased stiffness and decreased compliance. LV = left ventricular.

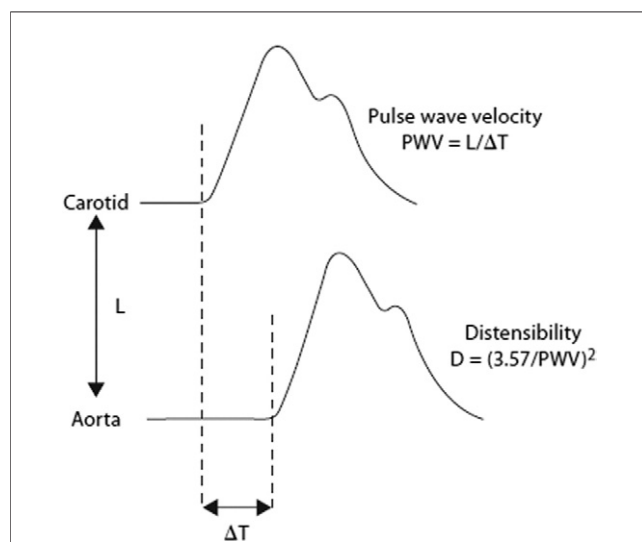


**Figure 3** Estimation of an Age-Specific Reference Interval for PWV

Reprinted with permission from Khoshdel et al. (9). PWV = pulse wave velocity.

flattened by an external force. An excellent in-depth review of this technique can be found elsewhere (17).

With 2 different sites (carotid and femoral artery, for example), the oscillometric method measures noninvasively the pulse transit time from the pressure waveforms at the 2 sites and infers the velocity in the “conduit” (Fig. 5). Asmar



**Figure 4** Noninvasive Determination of PWV Between the Carotid Artery and the Terminal Aorta

Femoral artery is the terminal aorta. The measured distance is L. If  $\Delta T$  represents the time delay between the feet of the 2 waves, pulse wave velocity (PWV) =  $L/\Delta T$ . Distensibility might be then deduced from the Bramwell-Hill formula. Automatic PWV measurements are currently widely used. Reprinted with permission from Safar M. Atherosclerosis, large arteries and cardiovascular risk. In: Safar ME, Frohlich E, editors. *Advances in Cardiology*. Basel: Karger AG, 2007:1-18.

et al. (13) calculated PWV with the oscillometric method in more than 400 individuals with excellent intra- and inter-observer reproducibility and good correlation between the automatic and manual approaches.

Normal values in the typical adult of middle-age are 4 m/s in the ascending aorta, 5 m/s in the abdominal aorta and carotids, 7 m/s in the brachial artery, and 8 m/s in the iliac arteries (18).

Ideally, the transit time should be coupled to a precise and reproducible measurement of true vascular lumen length. An important limitation to this method is that, because no vascular imaging is performed, the vascular length traveled by the pulse wave (i.e., the carotid to femoral distance) has to be approximated from a body surface measurement. Rigid measurements with calipers are monodimensional and do not take into account the 3-dimensional morphology of the aorta, carotid and femoral arteries (particularly in the anteroposterior direction) or the potential tortuosity associated with older arteries. This is also true for flexible tape measures, and it is a major argument in favor of making such distance measurements on a comprehensive aortic imaging dataset, such as those available with MRI. Direct intravascular distance measurements will always be much better than indirect external approximations.

Carotid-femoral pulse wave velocity (CFPWV) is considered to be a global estimate of arterial PWV through the entire aorta. However, we should note that this PWV is measured between 2 peripheral sites, with flow in the carotid and femoral arteries being in opposite directions, whereas the ascending aorta—a prime location of aortic stiffening—is not directly accounted for in this approach.

Another important caveat to this method is the amplification phenomenon. This phenomenon occurs because the



**Table 1** Noninvasive Methods to Assess Aortic Stiffness

Diagnostic Tool	Advantages	Disadvantages
Applanation tonometry	<ul style="list-style-type: none"> <li>No radiation exposure to the patient.</li> <li>Relatively inexpensive, easy to use and reproducible.</li> <li>Excellent portability and temporal resolution.</li> <li>Large amount of evidence supporting clinical significance and prognostication.</li> </ul>	<ul style="list-style-type: none"> <li>Accuracy becomes problematic because no true measurement of vascular lumen length is obtained between the 2 recording sites (overestimation of PWV can be particularly inaccurate in obese patients).</li> </ul>
Echocardiography	<ul style="list-style-type: none"> <li>Same as for applanation tonometry.</li> <li>Identification of other associated changes such as left ventricular hypertrophy, impaired diastolic function, and so on.</li> <li>Tissue Doppler and strain imaging can provide further information on pre-clinical changes of aortic elastic properties (21,22).</li> </ul>	<ul style="list-style-type: none"> <li>Not as extensively studied and validated as applanation tonometry.</li> <li>Echocardiography windows could be challenging in patients with advanced emphysema, morbid obesity, breast implants, and so on.</li> <li>Particularly in young subjects, pulse pressure amplification phenomenon occurs between central and peripheral arteries. Thus, inaccuracy can result in whichever method with brachial pulse pressure as a surrogate for aortic or carotid pulse pressure (i.e., echocardiography, CMR, and so on).</li> </ul>
CMR	<ul style="list-style-type: none"> <li>No ionizing radiation to the patient.</li> <li>Full 3-dimensional visualization of the vessel permits the imaging plane to be placed perpendicular to the vessel in a reproducible location.</li> <li>Assessment of both local distensibilities and regional pulse wave velocities at different locations of the arterial tree (regional stiffness).</li> <li>Other aspects—such as aortic wall strain, deformation, and so on—can also be evaluated.</li> </ul>	<ul style="list-style-type: none"> <li>Longer examination duration.</li> <li>Not feasible yet for patients with certain cardiac devices (pacemakers, defibrillators, and so on).</li> </ul>

CMR = cardiac magnetic resonance; PWV = pulse wave velocity.

pressure wave is progressively amplified due to increased wave reflections in smaller, less elastic, and more muscular distal arteries. Thus, it is inaccurate to use brachial pulse pressure as a surrogate for aortic or carotid pulse pressure, particularly in young subjects (4).

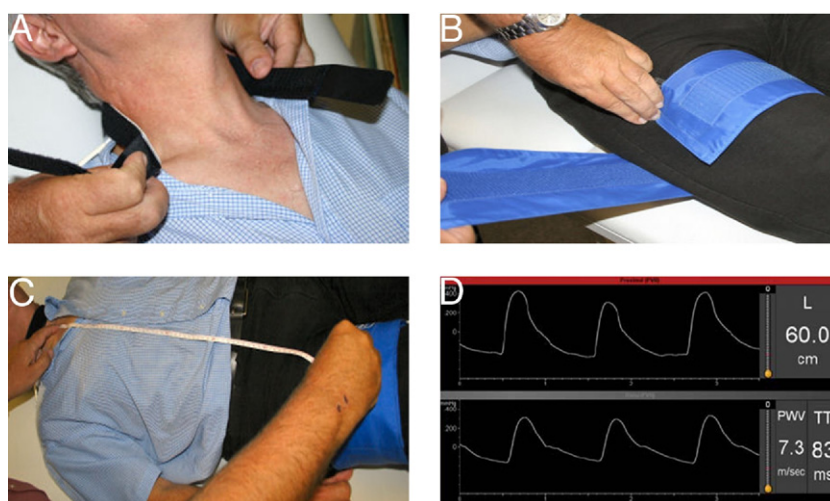
#### Measurement of AS and distensibility by echocardiography.

Pulse wave velocity can also be assessed noninvasively by echocardiography with pulse wave Doppler. Although this method has not been as commonly used, it seems to have good correlation ( $r = 0.83$ ) with the applanation tonometry (19). Furthermore, pulse wave Doppler allows quantification of

regional PWV, which could be advantageous as a future research tool (20). The main advantage of ultrasound techniques is their wide availability, and the main limitation is the incomplete visualization of the aortic arch.

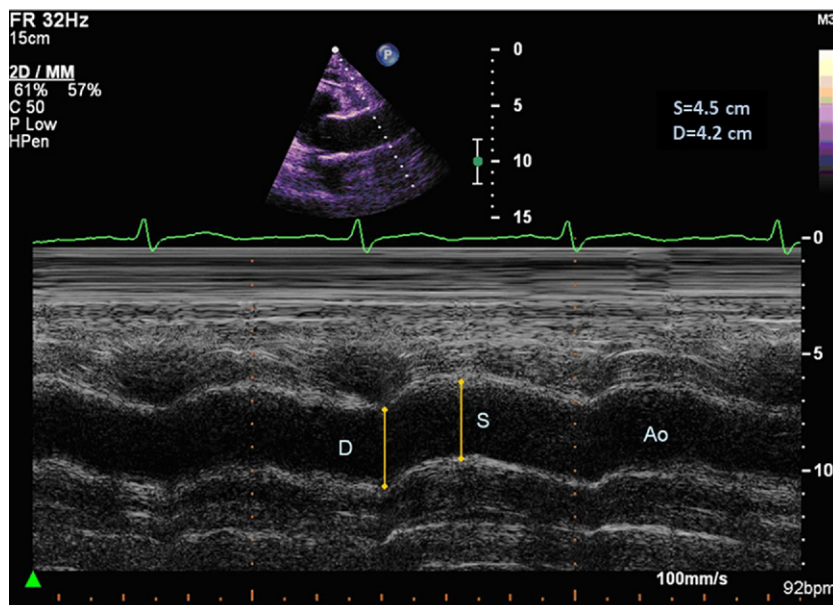
Aortic stiffness has also been evaluated with advanced echocardiography techniques such as tissue Doppler and strain imaging in different populations (21,22). These techniques are important research tools, with future clinical applications remaining to be found.

Furthermore, assessment of AD by transthoracic and transesophageal echocardiography has a high degree of



**Figure 5** Measurement of Aortic Stiffness by Carotid-Femoral Oscillometric Signal

(A) Neckpad placement; (B) thigh cuff placement; (C) aortic path length measurement; (D) pulse wave velocity (PWV) analysis is displayed on the computer screen. Reproduced with permission from Skidmore Medical, Ltd., Bristol, United Kingdom.



**Figure 6** Measurements of Aortic Diameters Shown on the M-Mode Tracing

Measurements of aortic diameters shown on the M-mode tracing obtained at a level 3 cm above the aortic cusps.  
Ao = aorta; D = diastolic aortic diameter; S = systolic aortic diameter.

accuracy when compared with invasive measurements, in different populations (23). On transthoracic echocardiography, M mode measurements are obtained at 3 cm above the aortic valve on parasternal long-axis view (Fig. 6) (24). On transesophageal echocardiography, measurements are done at the level of pulmonary artery bifurcation (2 to 3 cm above the aortic valve) and in the descending thoracic aorta just distal to the branching site of the left subclavian artery (25). The following formula, described by Stefanadis *et al.* (23), is then applied:

$$\text{Aortic Distensibility (in cm}^2\text{dyne}^{-1}\text{10}^{-6}\text{)} = \frac{2 \times (\text{systolic diameter} - \text{diastolic diameter})}{(\text{diastolic diameter}) \times (\text{brachial pulse pressure})}$$

As mentioned previously, pulse pressure amplification might confound these estimations when using brachial pulse pressure, especially in young individuals.

**Measurement of AS by MRI.** Unlike CFPWV, which is an average measure of overall arterial stiffness, MRI enables the detection of more subtle changes in regional stiffness. Magnetic resonance imaging has several advantages over ultrasound in that full 3-dimensional visualization of the vessel is possible, enabling the imaging plane to be placed perpendicular to the vessel in a reproducible location. This is an obvious advantage for the measurement of distensibility measured in MRI as a change in 2-dimensional vessel perimeter or area instead of 1-dimensional vessel diameter. Furthermore, velocity data can be acquired simultaneously within 1 acquisition plane in 2 aortic locations, and the path

length (distance between the 2 aortic locations) can be measured precisely.

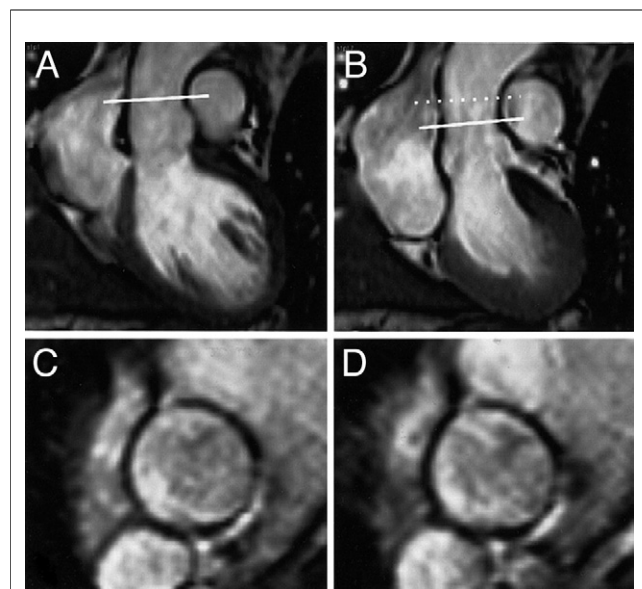
To assess AD by MRI, steady-state free precession cine imaging with electrocardiographic gating can be used to measure the changes in cross-sectional aortic area after aortic contouring, with a temporal resolution of  $<40$  ms. Alternatively, the modulus images of a similarly placed cine gradient echo phase contrast velocity acquisition can be used for aortic contouring and area measurements (26). The minimum and maximum ascending aortic cross-sectional areas should be measured and AD calculated as the following:

$$\text{Aortic Distensibility (in cm}^2\text{dyne}^{-1}\text{10}^{-6}\text{)} = \frac{\text{maximum area} - \text{minimum area}}{\text{minimum area} \times \Delta P \times 1,000}$$

where  $\Delta P$  is the pulse pressure in mm Hg (27).

Grotenhuis *et al.* (28) obtained AD measurements by MRI in patients with bicuspid aortic valves and showed significantly reduced aortic elasticity throughout the entire thoracic aorta when compared with control subjects (Fig. 7). Moreover, it is favorable to use central aortic pressures instead of brachial pressures to calculate distensibility to minimize the amplification phenomenon.

Velocity-encoded MRI with phase contrast sequences allows accurate assessment of the blood flow velocity with a sufficient temporal and spatial resolution to study the propagation of the aortic systolic flow wave. Velocity-encoded MRI, when compared directly with invasive hemodynamic measurements, had excellent correlation and



**Figure 7** Distensibility Measurement of the Aortic Root With Cardiac MRI

(A and B) Taken in the oblique coronal plane, these images show the slice positioning of the acquisition planes at minimal and maximal aortic flow for distensibility measurements, respectively, thus correcting for through-plane motion of the aortic root during contraction. Note the difference in position of the aortic root in both images, because of cardiac motion. (C and D) Corresponding area measurements in the double oblique transverse orientation. MRI = magnetic resonance imaging. Reproduced with permission from Grotenhuis *et al.* (28).

reproducibility. A recent article by Redheuil *et al.* (16) compared several of these noninvasive techniques used for the assessment of the elastic properties of the aorta and reported aortic distensibilities with MRI with central pressures. Ascending aorta distensibility correlated strongly with aortic arch MRI-derived PWV ( $r = 0.73$ ,  $p < 0.0001$ ), and both indexes were more strongly and specifically related to aging than applanation tonometry-derived indexes (CFPWV, augmentation index) or carotid distensibility.

### Clinical Importance and Prognostic Value of AS

Carotid-femoral PWV, a global measure of AS, has been shown to be an independent predictor of coronary heart disease and stroke in healthy subjects and an independent predictor of mortality in the general population (29). Carotid-femoral PWV is also a predictor of future changes in systolic blood pressure (SBP) and future development of hypertension in healthy volunteers. Thus, it might have a role in identifying patients at risk of development of hypertension (30). Furthermore, increased arterial stiffness has been associated with increased morbidity and both all-cause and cardiovascular (CV) mortality in hypertensive patients (31,32). Cruickshank *et al.* (33) showed, in a multiethnic population of patients with impaired glucose tolerance and/or diabetes, that higher aortic PWV was able

to independently predict all-cause and CV mortality, more so than SBP. Mitchell *et al.* (34) recently showed in a large community-based cohort that only CFPWV predicted major CV events. Recently, a meta-analysis including more than 15,000 subjects confirmed that CFPWV is an independent predictor of adverse CV events and all-cause mortality. An increase of aortic PWV of 1 m/s raises CV risk by more than 10% (35). The 2007 European guidelines for the management of hypertension and guidelines for CVD prevention in clinical practice recommend, given all the aforementioned, aortic PWV as a test to assess target organ damage (36,37).

### AS in Other Different Disease States

**Association with atherosclerosis and calcification.** Arteriosclerosis and atherosclerosis share similar pathobiologic processes. Because the vessel wall is progressively injured, over a period of time, the vessel wall matrix and adjacent cells develop reparative inflammatory processes to prevent further damage. As a result, arterial wall calcification and increased stiffness will occur. Coronary artery calcification is associated with impaired aortic distensibility (38). Al-Mallah *et al.* (39) recently showed that thoracic aortic calcification is inversely correlated with thoracic AD.

**Chronic kidney disease and end-stage renal disease.** Increased global AS (measured by CFPWV) has independently been associated with reduced creatinine clearance in subjects with mild to severe renal insufficiency, regardless of mean arterial pressure and other CV risk factors (40). Renal patients have marked reduction in AD along with disturbances in diastolic blood flow in the aorta contributing to reduced coronary perfusion (41).

**Diabetes mellitus.** Two recent small studies in type 2 diabetes mellitus patients have shown that diabetes mellitus is independently associated with lower AD, increased PWV, and impaired flow-mediated dilation when compared with age-, sex-, and comorbidities-matched control subjects (42,43). Results on MRI-measured distensibility of the ascending aorta from a large multiethnic cohort of healthy individuals confirmed that diabetic vascular alterations were predominant in younger individuals (44). In addition, increased AS has been shown to be an independent predictor of 10-year mortality in diabetic patients (33).

**Aortic regurgitation.** Patients with chronic aortic regurgitation and preserved systolic function have increased arterial distensibility. This could be due to greater vascular compliance needed as a compensatory mechanism to lessen the impact of the large systolic volume ejected into conduit arteries (45). The lack of this “compensatory distensibility” seems to be associated with faster hemodynamic deterioration and disease progression (46).

**Congenital heart disease (patients with bicuspid aortic valve and tetralogy of Fallot).** Individuals with bicuspid aortic valve have extensive changes in the extracellular matrix of the aortic media due to mutations in the FBN-1



gene. Experimental and clinical studies have demonstrated that decreased levels of FBN-1 are directly associated with higher levels of matrix metalloproteinases and aortic aneurysms, in similarity to what occurs in patients with Marfan's syndrome (47,48). Abnormal AS and distensibility are present in approximately 40% of patients with bicuspid aortic valve (49). Reduced aortic elasticity in bicuspid aortic valve patients has been associated with worsening aortic regurgitation and LV hypertrophy (28). These changes are likely related to genetically abnormal elastic fibers in a degenerated aortic medial layer. Further evidence for a genetic component is suggested, because bicuspid aortic valve is an autosomal dominant hereditary disease with low penetrance (50).

In addition, children after repair of tetralogy of Fallot also develop progressive aortic root dilation that seems to correlate with increased AS measured by PWV (51).

**Connective tissue disorders (Marfan syndrome and Ehlers-Danlos syndrome).** Patients with Marfan syndrome have genetic mutation in the FBN-1 resulting in aortic root dilation and subsequent aortic dissection. Increased aortic wall stiffness seems to start early in childhood and progresses with aging (52). Thus, tissue Doppler imaging can be used to assess alteration of aortic mechanics with good correlation and prediction for aortic dilation and dissection (53). Recently, losartan has been shown in small animal studies to blunt transforming growth factor-beta activation, decreasing its levels and preventing aortic root structural changes (54,55). Whether this becomes an effective treatment for Marfan syndrome patients is not clear.

Ehlers-Danlos syndrome is a group of conditions affecting collagen type III metabolism, causing hyperelasticity of joints and skin. The vascular type of Ehlers-Danlos is a rare disease presenting as spontaneous arterial rupture usually without dissection (56). A small study using MRI showed that AD was reduced, whereas aortic wall thickness was slightly increased, although only 9 of 15 subjects had interpretable images (57).

**After aortic coarctation repair.** A significant percentage of patients (20% to 40%) with successful repair of aortic coarctation will develop persistent hypertension at rest and during exercise. With cardiac MRI, Ou et al. (58) demonstrated that in normotensive post-coarctation repair patients, the pre-coarctation segments continued to express increased AS by PWV when compared with the post-coarctation segments. Perhaps this could contribute to aneurysmal changes seen after repair.

**Hypertrophic cardiomyopathy.** Patients with hypertrophic cardiomyopathy have significantly increased AS when compared with normal control subjects. The presence of macroscopic myocardial fibrosis (seen as areas of myocardial delayed-enhancement in MRI after gadolinium injection) is associated with further increase in AS and might adversely affect LV performance (59). Whether AS could be another parameter for risk stratification in these patients is unknown.

## Pharmacological Interventions on AS

Several studies showed that many antihypertensive medications could improve AS, although the small sample size limits further generalization (60).

**Angiotensin-converting enzyme inhibitors.** Benetos et al. (61) demonstrated a favorable decrease in the CFPWV after both acute (3 h after first dose) and chronic administration (after 15 days) of ramipril. Other studies have shown similar findings with different drugs within the same class (62,63). The mechanism is related to the reduction of the wave reflection and augmentation index (64) with subsequent lowering of SBP and less adverse LV remodeling.

**Angiotensin-2 receptor blockers.** The role of angiotensin-2 receptor blockers on AS is not yet clear, given the small number of studies including limited sample sizes. Two larger studies are underway to evaluate the effects on arterial stiffness of telmisartan alone or in combination with ramipril (65,66).

**Beta-blockers.** The REASON (Regression of Arterial Stiffness in a Controlled Double-Blind Study) compared perindopril (2 mg/day) plus indapamide (0.625 mg/day) versus atenolol (50 mg/day) alone for 12 months in hypertensive subjects. At 1 year, brachial and central SBP reduction achieved with combination therapy of angiotensin-converting enzyme inhibitor plus diuretic was greater than that with beta-blocker alone or even angiotensin-converting enzyme inhibitor alone. This effect was translated into greater structural changes of arterial stiffness more pronounced in central than in peripheral arteries (67). Higher CFPWV was closely correlated with higher SBP as a marker of more resistant hypertension requiring greater antihypertensive doses. In other words, increased arterial stiffening might be the reason of poor SBP response to drug treatment (68). Nebivolol, which is a selective beta-1 blocker with nitric oxide potentiating vasodilatory effect, has been shown to slightly decrease the augmentation index, when compared with atenolol (69). Whether this would result in favorable outcomes remains to be determined.

Moreover, it is important to highlight that the heart rate-lowering effect of beta-blockers has a major impact on the relationship between AS and central aortic pressure. As heart rate decreases, LV filling increases, inevitably enhancing aortic pulse augmentation (ventricular-vascular coupling). Thus, in individuals with stiffened aorta (higher aortic PWV), there is an inability of buffering the increased stroke volume, which translates into less effective central aortic pressure reduction seen with beta-blockers (70).

**Calcium-channel blockers.** The largest study to investigate the effect of calcium-channel blockers on pulse pressure is the CAFE (Conduit Artery Function Evaluation) study (71), which examined the impact of 2 different blood pressure-lowering regimens (atenolol  $\pm$  thiazide vs. amlodipine  $\pm$  perindopril) on derived central aortic pressures and hemodynamic status in 2,073 participants with hypertension and at least 3 additional risk factors. Although similar effects in the brachial blood pressure were seen, central



aortic pulse pressure was significantly lower with amlodipine  $\pm$  perindopril compared with atenolol  $\pm$  thiazide-based therapy. As previously mentioned, this could be predominantly determined by the beta-blockers effects on heart rate and stroke volume. No differences were seen in the small subgroup ( $n = 114$ ) who had CFPWV measurements (71).

**Statins.** The role of statins in AS remains controversial. Some studies have not shown important improvements in aortic hemodynamics (72). Nevertheless, a few small randomized placebo-control studies, in different populations, have shown that statins decrease the inflammatory marker levels in addition to having favorable effects on AD (73–75). In addition, rosuvastatin has been shown to reduce 3-nitrotyrosine levels (a marker of peroxynitrite-mediated oxidative stress) and to decrease aortic PWV. Interestingly, reduction of plasma cholesterol was the only independent predictor of reduced arterial stiffness in patients with primary hypercholesterolemia after rosuvastatin therapy (76).

**Cross-link breakers.** Advanced glycation end product formation, which occurs with aging and diabetes, has been implicated in increased myocardial and vascular stiffness (Fig. 2). Advanced glycation end product cross-link breakers have emerged as a potential therapeutic target. Alagebrium has been extensively studied in phase I and II studies showing good safety and tolerability profile (77).

Kass *et al.* (78) demonstrated that alagebrium significantly improved arterial compliance, CFPWV, and pulse pressure after 8 weeks of treatment in elderly patients with baseline vascular stiffening. These changes occurred without disproportionate decline in mean arterial pressure, systemic resistance, cardiac output, or heart rate. Further studies exploring other applications such as heart failure with preserved systolic function and arterial hypertension have also been considered (79).

### Nonpharmacological Interventions on AS

Several nonpharmacological interventions to reduce AS are currently being investigated. The 2 most important areas are: aerobic exercise training and continuous positive airway pressure (CPAP).

**Aerobic exercise training.** Aerobic exercise training produces several beneficial changes that have been well-reviewed elsewhere (80). Although its direct effects on AS and diastolic function have not yet been completely understood, indirect evidence seems to indicate favorable changes in aortic hemodynamic status with both acute and chronic exercise training (81).

Retrospective studies have shown that increased physical activity is correlated with improved aortic PWV when compared with age-matched sedentary control subjects (82,83). Hundley *et al.* (84) have shown that older patients with isolated diastolic heart failure have impaired AD (beyond that which occurs with normal aging) that correlates with and might contribute to severe exercise intolerance. More importantly, reduced AD might also be a

plausible explanation for exaggerated hypertensive response to exercise long before hypertension is overtly manifested (85). Another study compared the impact of different types of aerobic exercise training on AD. Arterial stiffness was higher in strength-trained men compared with endurance-trained men and sedentary control men. These findings were directly correlated to higher levels of endothelin-1. Controversy still exists, because other studies in healthy normotensive men have suggested that chronic resistance training has detrimental effects on central arterial compliance and LV remodeling (86). Thus, it seems that different exercise training modalities (endurance vs. resistance training) and their duration (acute vs. chronic) have different effects on vascular tone (87).

**CPAP.** Systemic arterial stiffness has been positively correlated with the severity of obstructive sleep apnea of worse magnitude during the early hours of the day (88,89). How CPAP alters systemic hemodynamic status continues to be a subject of investigation, but recent studies have proposed a couple of potential mechanisms. CPAP seems to improve arterial stiffness and central blood pressure by a combination of enhanced endothelial function and reduction in sympathetic tone. CPAP treatment also increases nitric oxide production in patients with obstructive sleep apnea (90). A recent article by Phillips *et al.* (91) showed that significant reduction in arterial stiffness and central blood pressure occurred after initiation of CPAP. More importantly, these findings were reversed after withdrawal from this therapy, indicating an important link.

### Future Perspectives

Aortic stiffness is now recognized as an important determinant of CV morbidity and mortality. However, the plethora of studied and reported markers of AS, the differing modalities used to assess aortic mechanics, and the complex interplay among measures of blood pressure and LV dynamics (coupling) have somewhat hampered the current clinical impact and further development of this field. Furthermore, one of the major difficulties in interpreting changes in AS is the impact that different therapies have on blood pressure and heart rate. Most of these studies have been retrospective or subgroup analysis of larger clinical trials. In addition, surrogate rather than hard CV end points are often used; therefore, properly powered and controlled trials are needed to better identify effective strategies associated with improvement of aortic stiffness.

Other perspectives are also worth considering for future research in this field:

1. Larger sample studies—the statistical power for detecting significant differences in treatment groups should be discerned more clearly.
2. Combining pharmacological and nonpharmacological strategies might provide greater impact in reversing AS, particularly in special populations.

3. Creating a standard methodology for measuring PWV and a larger normative database with threshold values. Recently, reference and normal values for PWV from a large multicenter European cohort (n = 11,092) were published (92). This is a major step forward and should motivate similar efforts from other major scientific societies and expert committees. Furthermore, establishing age- and perhaps sex-related percentiles with cutoff points for each technique, similar to what has been done for coronary calcification assessment, could facilitate the future use of AS as an end point in large clinical trials.

## Conclusions

Increased arterial stiffness is an important marker of increased LV load and a predictor of CV morbidity that might precede the onset of systemic hypertension in humans. Currently, several pharmacological therapies have been shown to improve AS and mechanics. However, the vast majority of trials to date were uncontrolled and/or had limited sample sizes (i.e., <100 participants). Nonpharmacological approaches such as aerobic exercise training and CPAP in small studies have also shown favorable results. Future studies testing the summation of these strategies are needed, because a greater magnitude of response might occur, altering this important CV disease phenotype.

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**Key Words:** aortic distensibility ■ aortic stiffness ■ applanation tonometry ■ pulse wave velocity.