

## ATVB In Focus

## Noninvasive Assessment of Atherosclerosis: from Structure to Function

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- Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. 2003;23:168–175.

## Noninvasive Assessment of Arterial Stiffness and Risk of Atherosclerotic Events

James J. Oliver, David J. Webb

**Abstract**—Investigation of arterial stiffness, especially of the large arteries, has gathered pace in recent years with the development of readily available noninvasive assessment techniques. These include the measurement of pulse wave velocity, the use of ultrasound to relate the change in diameter or area of an artery to distending pressure, and analysis of arterial waveforms obtained by applanation tonometry. Here, we describe each of these techniques and their limitations and discuss how the measured parameters relate to established cardiovascular risk factors and clinical outcome. We also consider which techniques might be most appropriate for wider clinical application. Finally, the effects of current and future cardiovascular drugs on arterial stiffness are also discussed, as is the relationship between arterial elasticity and endothelial function. (*Arterioscler Thromb Vasc Biol.* 2003;23:554–566.)

**Key Words:** arterial stiffness ■ noninvasive assessment ■ endothelial function ■ cardiovascular risk stratification ■ pulse wave analysis

### Arterial Stiffness

Data from the Framingham Heart Study have determined how systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP; the difference between SBP and DBP) change with advancing age.<sup>1</sup> DBP, largely determined by peripheral arterial resistance, increases until middle age and then tends to fall. In contrast, SBP and PP, influenced more by the stiffness of large arteries, as well as peripheral pulse wave reflection and the pattern of left ventricular ejection, increase continuously with age. Changes in the stiffness of the large arteries, such as the aorta and its major branches, largely account for the changes in SBP, DBP, and PP that occur from 50 years of age onward. Although DBP has traditionally been the major focus in the treatment of hypertension, over recent years SBP has become recognized as a stronger cardiovas-

cular risk factor in older people. Thus, SBP has greater predictive value than DBP for coronary heart disease (CHD) in older people (>60 years).<sup>2,3</sup> Isolated systolic hypertension (ISH; SBP  $\geq$ 140 mm Hg and DBP <90 mm Hg), is the most common subtype of hypertension in the middle aged and is overwhelmingly so in the elderly.<sup>4</sup> It is a major risk factor for stroke,<sup>5</sup> CHD,<sup>2,3</sup> and cardiovascular and total mortality.<sup>6,7</sup> Furthermore, measurement of SBP alone identifies >90% of hypertensives according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VI criteria, whereas DBP alone identifies only  $\approx$ 20%.<sup>8</sup> The treatment of ISH with conventional antihypertensive drugs is of proven clinical benefit.<sup>9,10</sup> However, although it is recognized that few hypertensives are controlled to target pressures,<sup>11</sup> it is much more commonly

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SBP than DBP that is not adequately controlled.<sup>4,8</sup> Although the importance of treating raised SBP is increasingly recognized in clinical practice, in recent years the brachial artery PP, the major determinant of which, in older people, is large artery stiffness, has emerged as an even stronger predictor of CHD,<sup>12</sup> although not consistently.<sup>13</sup> However, whether specifically targeting raised PP or arterial stiffness, rather than raised SBP, in the treatment of hypertension is of greater benefit is not known.

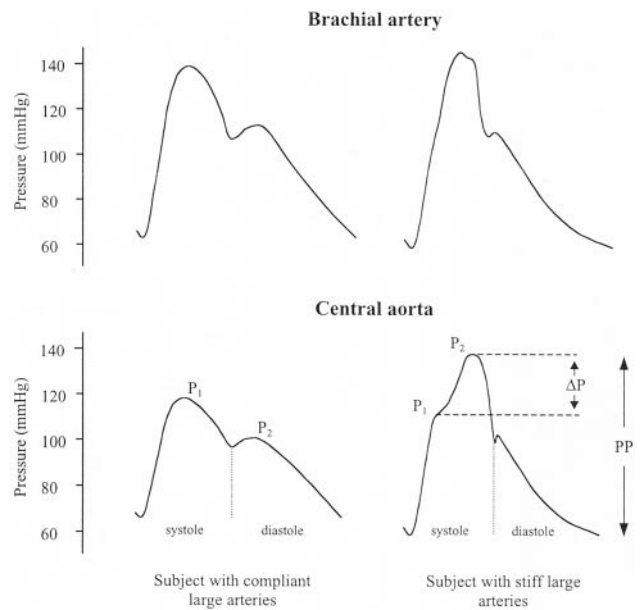
Hence, there is a strong rationale for understanding the mechanisms of arterial stiffness to better treat ISH. In addition, other established cardiovascular risk factors are also associated with increased arterial stiffness. Currently, there is a need to quantify the extent to which measures of arterial stiffness can improve risk stratification and to determine whether its reduction is capable of independently predicting clinical benefit in different at-risk populations.

Following an outline of the mechanisms of arterial stiffness, we discuss the methodologies available for the noninvasive assessment of arterial stiffness, including how the measured parameters relate to established cardiovascular risk factors and clinical outcome and indicate which might be most appropriate for wider clinical application. The effects of current and future cardiovascular drugs on arterial stiffness are also discussed, as is the relationship between arterial elasticity and endothelial function.

### Mechanisms of Arterial Stiffness

Windkessel theory treats the circulation as a central elastic reservoir (the large arteries), into which the heart pumps, and from which blood travels to the tissues through relatively nonelastic conduits (peripheral arteries). The elasticity of the proximal large arteries is the result of the high elastin to collagen ratio in their walls, which progressively declines toward the periphery. The increase in arterial stiffness that occurs with age<sup>14</sup> is largely the result of progressive elastic fiber degeneration.<sup>15</sup> It should be noted that terms such as large, proximal, and central arteries are frequently used without any precise definition. Here, we refer to the aorta and its major branches as large arteries, which can be differentiated from the more muscular conduit arteries, such as the radial and brachial, and the smaller predominantly muscular peripheral arteries.

The elasticity of a given arterial segment is not constant but instead depends on its distending pressure.<sup>14,16</sup> As distending pressure increases, there is greater recruitment of relatively inelastic collagen fibers<sup>17–19</sup> and, consequently, a reduction in elasticity. The background level of distending pressure in the circulation is determined by mean arterial pressure (MAP). This is important because MAP must be taken into account whenever measurements of arterial stiffness are made so that anticipated effects of distending pressure can be differentiated from real differences in the elasticity of the arterial wall. In addition to collagen and elastin, the endothelium<sup>20,21</sup> and arterial wall smooth muscle bulk and tone<sup>19,22</sup> (the latter under some control from the endothelium) also influence elasticity. A number of genetic influences on arterial stiffness have also been identified. Thus, polymorphic variation in the fibrillin-1,<sup>23</sup> angiotensin II type-1 receptor,<sup>24</sup> and endothelin



Schematic representation of pulse pressure amplification. Typical pressure tracings from the brachial artery and central aorta are shown. When the large arteries are compliant, such as in a normal healthy young subject (waveforms on the left), the arterial waveform is amplified as it travels toward the periphery. As the large arteries stiffen, for example, with increasing age, diabetes, or other cardiovascular risk factors, this amplification is reduced (waveforms on the right). The two subjects have similar BP at the brachial artery despite striking differences at the aorta, demonstrating the importance of assessing central BP in individuals. The effect of peripheral wave reflection on the central aortic waveform is illustrated in the lower tracings. When the large arteries are compliant the initial systolic pressure wave,  $P_1$ , traveling from the heart to the periphery, is responsible for peak SBP. Reflected pressure waves,  $P_2$ , arrive at the central aorta in diastole, augmenting DBP and coronary artery filling. As large arteries stiffen, wave reflection occurs earlier so that SBP is augmented and DBP falls. Alx is calculated as the difference between the second ( $P_2$ ) and first ( $P_1$ ) systolic peaks ( $\Delta P$ ) as a percentage of the PP. Thus, Alx is negative in healthy young people, but with aging or increasing cardiovascular risk, arteries stiffen and Alx becomes increasingly positive.

receptor<sup>25</sup> genes are related to stiffness. The angiotensin-converting enzyme (ACE) I/D polymorphism has been associated with stiffness,<sup>26</sup> but not consistently.<sup>24</sup>

Ejection of blood from the left ventricle during systole initiates an arterial pressure wave that travels toward the periphery. At points of impedance mismatch, chiefly at the high-resistance arterioles, wave reflection occurs.<sup>27</sup> As a consequence of differing elastic qualities and wave reflection, the shape of the arterial waveform varies throughout the arterial tree. In healthy, relatively young subjects, whereas MAP declines SBP and PP are amplified in the peripheral circulation (Figure).<sup>28</sup> This amplification is exaggerated during exercise<sup>29</sup> but reduces with increasing age.<sup>30</sup> Although peripheral blood pressure (BP) is most commonly measured, the information contained within the waveform of the proximal aorta is of particular interest because it is the BP profile at this site, rather than more peripherally, that determines left ventricular load and coronary blood flow. The effects of increased arterial stiffness on the central aortic waveform and BP are illustrated in the Figure. The contour and amplitude of

**TABLE 1. Definitions of Some Parameters Commonly Measured in the Assessment of Arterial Stiffness**

Parameter	Definition	Formula
Compliance	The absolute change in vessel diameter (or area) for a given change in pressure	$\Delta D/\Delta P$ $\Delta A/\Delta P$
Compliance, capacitive ( $C_1$ )	Relationship between decline in pressure and decline in volume in the arterial tree during the exponential component of diastolic pressure decay (said to reflect large artery compliance)	$\Delta V/\Delta P$
Compliance, oscillatory ( $C_2$ )	Relationship between oscillating pressure change and oscillating volume change around the exponential pressure decay during diastole (said to reflect small artery compliance)	$\Delta V/\Delta P$
Distensibility	The relative change in vessel diameter (or area) for a given change in pressure	$\Delta D/(\Delta P \times D)$ $\Delta A/(\Delta P \times A)$
Elastic modulus	The pressure change required for (theoretical) 100% stretch from resting diameter (inverse of distensibility)	$(\Delta P \times D)/\Delta D$
Pulse wave velocity	The speed with which the pulse wave travels along a length of artery	Distance/ $\Delta t$
Stiffness index ( $\beta$ )	The ratio of the natural logarithm of SBP/DBP to the relative change in diameter	$\ln(P_s/P_d)/$ $[(D_s - D_d)/D_d]$
Young's modulus (incremental elastic modulus)	Elastic modulus per unit area (accounts for wall thickness)	$(\Delta P \times D)/(\Delta D \times h)$

Definitions of some of the parameters commonly measured in the assessment of arterial stiffness: D indicates diameter; P, pressure; A, area; V, volume; t, time; s, systole; d, diastole; h, wall thickness. Augmentation index (AIx) is defined in Figure 1.

the pressure waveform are influenced by large artery pulse wave velocity (PWV), in that faster traveling pressure waves arrive at, and are reflected from, the peripheral circulation earlier. When arteries are relatively compliant and PWV is relatively slow, reflected waves return to the central aorta in diastole, augmenting DBP and, therefore, coronary blood flow, which occurs predominantly during diastole. When arteries are stiffer and PWV is higher, reflected waves arrive earlier and augment central SBP, rather than DBP, increasing left ventricular workload and compromising coronary blood flow.<sup>31,32</sup>

### Noninvasive Methodologies for the Assessment of Arterial Stiffness

Many methodologies, both invasive and noninvasive, have been applied to the assessment of arterial elasticity *in vivo*. Noninvasive measures fall into three broad groups: 1) measuring PWV, 2) relating change in diameter (or area) of an artery to distending pressure, and 3) assessing arterial pressure waveforms. Definitions of the parameters commonly measured are listed in Table 1. There is a large and rapidly expanding number of published studies investigating how the various noninvasive measures of arterial stiffness are related to both cardiovascular risk factors and prognosis and are influenced by different treatments. Thus, in addition to describing the major existing technologies and highlighting their important limitations, here we summarize and interpret this growing literature.

### Pulse Wave Velocity (PWV)

Interest in, and measurement of, the velocity of arterial wave propagation as an index of vascular stiffness and vascular health dates back to the early part of the last century.<sup>33</sup> The arterial PWV, especially of the aorta, has emerged as an important independent predictor of cardiovascular events. PWV increases with stiffness and is defined by the Moens-Korteweg equation,  $PWV = \sqrt{(Eh/2\rho R)}$ , where  $E$  is Young's modulus of the arterial wall,  $h$  is wall thickness,  $R$  is arterial

radius at the end of diastole, and  $\rho$  is blood density. There are a number of different ways to measure PWV, and these are generally simple to perform. The arterial pulse wave is recorded at a proximal artery, such as the common carotid, as well as at a more distal artery, such as the femoral. The superficial location of the carotid and femoral arteries means that their pulse waveforms are readily measured noninvasively, and between these 2 sites the pulse wave has to travel through most of the aorta, an artery particularly prone to the development of atherosclerosis. The time delay between the arrival of a predefined part of the pulse wave, such as the foot, at these 2 points is obtained either by simultaneous measurement, or by gating to the peak of the R-wave of the ECG. The distance traveled by the pulse wave is measured over the body surface and PWV is then calculated as distance/time (m/s). The measured distance is an estimate of the true distance traveled and depends to some extent on body habitus. Furthermore, the abdominal aorta tends to become more tortuous with age,<sup>34</sup> potentially leading to an underestimation of PWV. Arterial pulse waves can be detected by using pressure-sensitive transducers,<sup>35</sup> Doppler ultrasound (the pressure pulse and the flow pulse propagate at the same velocity),<sup>36</sup> or applanation tonometry,<sup>37</sup> where the pressure within a small micromanometer flattened against an artery equates to the pressure within the artery.

Aortic PWV can also be measured noninvasively by using MRI.<sup>38</sup> MRI has the potential advantage of accurate determination of path length, although factors, such as the time required to make a recording, lack of availability in the immediate clinical setting, relatively high cost per measurement, and the difficulty in performing clinical studies within a strong magnetic field, mean that few studies have been performed with this technique. However, a recent study showed that MRI offers insights not otherwise possible, in describing greater age-related increase in PWV in the proximal than in the distal aorta.<sup>39</sup>

Increases in distending pressure increase PWV.<sup>33</sup> Therefore, account should be taken of the level of BP in studies that use

PWV as a marker of cardiovascular risk or as a measure of the effects on arterial stiffness of interventions that reduce BP. Heart rate has also been reported to influence PWV. In one study an increase in heart rate of 40 beats per minute increased PWV by  $>1$  m/s,<sup>40</sup> a difference that may be relevant to the assessment of cardiovascular risk. However, it has been suggested this finding may be an artifact of the methodology used.<sup>41</sup>

Raised PWV occurs with a range of established cardiovascular risk factors,<sup>42</sup> including age,<sup>43,44</sup> hypercholesterolemia,<sup>45</sup> type II diabetes,<sup>46</sup> and sedentary lifestyle.<sup>44</sup> In hypertension, carotid–femoral PWV is an independent predictor of both cardiovascular and all-cause mortality.<sup>47</sup> The odds ratio for a 5 m/s increment in PWV was 1.34 for all-cause mortality and 1.51 for cardiovascular mortality. In contrast, PP was independently related to all-cause mortality but only marginally related to cardiovascular mortality, indicating that specific assessment of arterial stiffness, with PWV, may be of greater value in the evaluation of risk. It should be noted that 5 m/s is a relatively large change in PWV. In this study PWV ranged from 9 to 13 m/s, whereas recently quoted values of carotid–femoral PWV in healthy individuals with average ages of 24 to 62 years ranged from around 6 to 10 m/s.<sup>48</sup> Differences between studies regarding the method used to calculate the distance traveled between the carotid and femoral sites probably explains some of the variation in these normal values.

In hypertensives without a history of overt cardiovascular disease PWV also predicts the occurrence of cardiovascular events independently of classic risk factors.<sup>49</sup> Once again, PP was of predictive value in univariate but not multivariate analysis. Aortic PWV  $>13$  m/s is a particularly strong predictor of cardiovascular mortality in hypertension.<sup>50</sup> Recently published data show that carotid–femoral PWV increases at a faster rate in treated hypertensives than in normotensive controls, although where BP was well controlled PWV progression was attenuated.<sup>51</sup> High heart rate and plasma creatinine  $>8$  mg/L were other determinants of accelerated progression of PWV in hypertensives in this study. Aortic PWV, assessed by using Doppler flow recordings, also independently predicts mortality in patients with end-stage renal failure (ESRF), a population with a particularly high rate of cardiovascular disease.<sup>52,53</sup> The benefit associated with BP control in ESRF, either by adjustment of dry weight or the use of antihypertensives, was independently related to change in aortic PWV, such that a reduction in PWV of 1 m/s was associated with a relative risk of 0.71 for all-cause mortality.<sup>54</sup>

### Relating Change in Vessel Diameter (or Area) to Distending Pressure

The change in diameter of a number of arteries, such as the carotid, brachial, radial, and aorta, can be related to the distending pressure, providing a series of direct measures of stiffness. Ultrasound is the most frequently used imaging modality, although MRI has been used rarely. Calculation of parameters, such as compliance and distensibility, requires that the incremental pressure of the artery in question be known, for example, the carotid PP. However, many authors have used BP measured at the brachial artery in these calculations<sup>55</sup> whereas, because of PP amplification, this may not represent the carotid artery PP. Furthermore, the extent of

PP amplification differs between individuals, so that comparing different groups by using stiffness parameters incorporating peripheral BP measurement may not be valid.

Alternatively, applanation tonometry can be used to assess carotid BP. Although this technique is not normally used to measure absolute pressure, the brachial artery MAP can be assumed to be equal to that in the carotid so that the absolute pressure of the carotid waveform can be calculated. Diameter–pressure curves over the systolic–diastolic range can thus be obtained with the simultaneous use of ultrasound and applanation tonometry. These diameter–pressure curves can then be used to derive distensibility–pressure curves. In this way, carotid artery distensibility has been investigated in hypertensives and matched controls.<sup>56</sup> For each group, distensibility was calculated at MAP ( $Dist_{MAP}$ ), which, naturally, is higher in hypertensives, and at 100 mm Hg ( $Dist_{100}$ ), a level of carotid BP common to both groups.  $Dist_{MAP}$  was lower in hypertensives, but  $Dist_{100}$  was similar in the two groups. These findings were confirmed in a subsequent study, at  $Dist_{MAP}$  and  $Dist_{110}$ .<sup>57</sup> The authors of the latter study also constructed curves of incremental elastic modulus ( $E_{inc}$ ) against circumferential wall stress. The cross-sectional area of the arterial wall and, therefore, its thickness, is accounted for in the calculation of  $E_{inc}$ . As a result,  $E_{inc}$  is independent of arterial geometry and may be considered a measure of the intrinsic stiffness of the arterial wall material. In keeping with the findings for distensibility,  $E_{inc}$  increased with stress during the cardiac cycle and was higher in hypertensives at their respective mean circumferential wall stresses, but overall there were no differences between the groups for common wall stress values. An alternative approach proposed to characterize the elastic properties of arteries independently of distending pressure is to calculate the stiffness index,  $\beta$ . Reducing SBP by up to 40 mm Hg with sodium nitroprusside infusion in 8 patients with myocardial infarction led to a reduction in elastic modulus, a parameter that is dependent on distending pressure, but had no effect on  $\beta$ .<sup>58</sup> Although further validation of  $\beta$  is desirable, elastic modulus of the carotid artery was increased in hypertensives compared with controls, but  $\beta$  was similar in the 2 groups.<sup>59</sup> In a subsequent study, elastic modulus was related to left ventricular hypertrophy, whereas  $\beta$  was related to concentric remodeling but not hypertrophy.<sup>60</sup> These data indicate that, at least at the carotid artery, distending pressure alone may account for reduced arterial elasticity in hypertension.

In contrast, aging appears to have different effects on carotid artery stiffness. Increased age correlated with reduced  $Dist_{100}$ ,<sup>56</sup> suggesting that structural or functional changes other than those simply associated with greater distending pressure, account for the aging-associated reduction in arterial distensibility.  $E_{inc}$  at common circumferential wall stress increased with age in both hypertensives and controls, and in middle-aged and older subjects there was no difference related to BP.<sup>57</sup> However, younger hypertensives had a higher  $E_{inc}$  for a given wall stress. These findings suggest that in hypertension the material of the arterial wall is intrinsically stiffer only in young subjects, and that age-related, rather than hypertension-related changes become more important in later life.

Pressure–diameter relationships can be accurately determined invasively with simultaneous measurement of arterial pressure by using a luminal pressure transducer and dimensions by using intravascular ultrasound. In a similar manner to the noninvasive methods, this technique can differentiate the effects on elasticity of distending pressure from the intrinsic properties of the vessel wall. The use of this technique in reducing aortic distensibility has been demonstrated with increased age,<sup>61</sup> in patients with CHD,<sup>62</sup> hypertension<sup>61,63</sup> and hypercholesterolemia,<sup>61</sup> and acutely after smoking.<sup>64</sup> This technology has not been applied to the carotid artery, although such studies would help to determine the reliability of the non-invasive techniques.

Although few studies have related local noninvasive measures of arterial stiffness to clinical outcome, carotid artery stiffness is a predictor of mortality in patients with ESRF. Thus, in prospective studies,  $E_{inc}$  emerged as the strongest independent determinant of all-cause mortality in 79 patients<sup>65</sup> and also independently predicted mortality risk in a larger sample of 110 patients with ESRF.<sup>66</sup> Carotid artery distensibility was also an independent predictor of cardiovascular events after renal transplantation, although in this study BP was measured at the brachial artery.<sup>67</sup>

MRI can also be used to measure arterial, usually aortic, distensibility noninvasively, although its value is probably limited to small mechanistic studies. In healthy subjects MRI revealed compliance to be greater in the ascending aorta than the aortic arch where, in turn, it was greater than in the proximal descending aorta.<sup>68</sup> Aortic compliance was greater in athletes and lower in patients with CHD compared with matched controls.<sup>68</sup> Aortic distensibility was reduced in hypertensives, whether measured at the ascending, descending thoracic or abdominal aorta,<sup>69</sup> but differences in distending pressure (MAP) were not accounted for in either of these studies. Proximal aortic distensibility decreased with age and was also less in patients with diastolic heart failure, in whom it was an independent predictor of exercise capacity.<sup>70</sup> A limitation of all of these studies is that measures of peripheral, rather than central, BP were used in the calculation of distensibility or compliance.

## Analysis of the Arterial Pulse Waveform

### *Systolic Pulse Contour Analysis (SPCA)*

Analyses of specific components of the arterial pressure or flow waveform are used by a number of noninvasive methodologies designed to measure arterial stiffness. Peripheral artery pressure waveforms can be acquired noninvasively by using applanation tonometry. When measured at the radial artery the waveform is calibrated to conventionally measured brachial BP. SPCA uses a transfer function to derive central aortic waveforms from those obtained from a peripheral artery, most commonly the radial. From the central aortic waveform central BP values and the augmentation index (AIx; Figure) can be calculated. The AIx is the proportion of central PP that results from arterial wave reflection and is a commonly used measure of arterial stiffness. Although the timing of the arrival of the reflected wave at the proximal aorta is largely determined by large artery PWV, AIx is not simply a surrogate measure of PWV. It is influenced by vasoactive drugs independently of PWV,<sup>71</sup> suggesting that it is

also determined by the intensity of wave reflection which, in turn, is determined by the diameter and elasticity of small arteries and arterioles. AIx increases with MAP<sup>72</sup> and is inversely related to heart rate<sup>73,74</sup> and body height,<sup>75</sup> so these variables should be accounted for when interpreting studies that use SPCA. Twin studies suggest that AIx is partly heritable, independent of these variables.<sup>76</sup> SPCA is simple, rapid, and can be used in the clinical as well as research setting.

Rather than individualizing the transfer function for particular subject characteristics, SPCA uses a generalized transfer function in all situations. This has been subject to a number of validation studies. It was reasonably accurate in determining central aortic waveforms at rest in patients with CHD.<sup>77</sup> In a study that measured radial waveforms with tonometry and aortic waveforms invasively, individualizing the transfer function added little to the accuracy of determining central BP and AIx, even after hemodynamic challenges such as the Valsalva maneuver and infusion of nitroglycerine.<sup>78</sup> However, more recently it has been suggested that gender-specific transfer functions may be more reliable than a generalized transfer function.<sup>79</sup> The use of invasive recordings at the aorta and radial artery in patients with angina showed that the generalized transfer function tended to underestimate aortic SBP by 6 to 8 mm Hg and overestimate aortic DBP by about 4 mm Hg.<sup>80</sup> In two studies<sup>81,82</sup> the correlation coefficient of directly-measured and reconstructed AIx was around 0.66 and, in both, reconstructed AIx tended to underestimate the measured value. Furthermore, the correlation was weaker after nitroglycerine administration, and inter-individual variation in the relationship of AIx obtained directly and from the reconstructed waveform was highlighted.<sup>82</sup> SPCA is increasingly used in healthy volunteer studies and it should be noted that the transfer function has not been validated in young subjects with compliant vessels. The generalized nature of the transfer function used in SPCA may represent a weakness of the technique that could benefit from further consideration. SPCA shows good reproducibility in both healthy subjects<sup>37</sup> and patients with ESRF.<sup>83</sup>

SPCA has been used to explain why peripheral DBP, rather than SBP or PP, is a better predictor of CHD risk in the young, whereas the strongest predictor of CHD risk in older people is peripheral PP.<sup>30</sup> In young subjects (<50 years), as DBP increases early wave reflection also increases, causing a reduction in peripheral PP amplification. In contrast, in older subjects amplification does not depend on DBP, perhaps because wave reflection is already increased due to age-related arterial stiffening. Therefore, for a given increase in DBP in younger subjects there is a greater rise in central SBP and PP than occurs in older people. In older subjects peripheral PP more accurately predicts central PP, although there is, of course, substantial individual variation. These findings regarding PP amplification may be relevant to the clinical management of young people with high peripheral SBP or PP. Even though these BP parameters are not important predictors of risk in this age group, performing SPCA may provide some reassurance that the peripheral pressures are the result of exaggerated PP amplification, with normal central SBP and PP, so that subjects are unlikely to gain from antihypertensive treatment.

SPCA has been performed in a number of at-risk populations. AIx increases with age<sup>84–86</sup> and, compared with matched controls, is also higher in patients with type I diabetes<sup>87</sup> and hypercholesterolemia,<sup>88</sup> despite similar peripheral BP. Thus far, there are no data on the prognostic value of AIx calculated from the central aortic waveform when derived from radial artery tonometry. However, SPCA has been incorporated into a number of prospective cohort studies with hard clinical endpoints, including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in hypertensives, the Edinburgh Artery Study in atherosclerosis, the Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine with Simvastatin and Folic Acid/Vitamin B12 (SEARCH), and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. AIx can also be directly measured by using applanation tonometry, relatively close to the central aorta, at the carotid artery. High carotid AIx is an independent predictor both of cardiac ischemic threshold during exercise in patients with CHD<sup>89</sup> and of all-cause and cardiovascular mortality in patients with ESRF.<sup>90</sup> Of particular note from the latter study, AIx predicted mortality even in patients considered to have a normal PWV (<11 m/s), highlighting the importance of assessing arterial wave reflection, rather than just arterial stiffness. In a further study on ESRF patients that used carotid artery tonometry, reduction in peripheral PP amplification, in addition to raised aortic PWV, also independently predicted all-cause mortality.<sup>53</sup>

#### *Diastolic Pulse Contour Analysis (DPCA)*

By using a modified Windkessel model, the analysis of the diastolic portion of the pressure pulse contour can be used to derive information on the compliance of both proximal and distal arteries. Two components of the diastolic waveform are distinguished in DPCA. An exponential decay curve represents large (capacitive) artery compliance, sometimes referred to as  $C_1$ . The other component, referred to variously as  $C_2$ , oscillatory compliance or reflective compliance, consists of peripheral wave reflections which are superimposed on the basic waveform and provide a measure of small artery compliance.<sup>91</sup> As with SPCA, the waveform of the radial artery can be determined noninvasively by using tonometry and calibrated for BP by using standard sphygmomanometry, potentially allowing for wide clinical application. Values obtained by using the noninvasive methodology have been compared with those obtained from waveforms obtained invasively.<sup>92</sup> Tonometry-measured pressure tended to underestimate, but was tightly correlated to, pressure determined invasively. The waveform obtained by using tonometry also exhibited fewer high frequency components compared with that obtained invasively. Compliance calculated from invasive and noninvasive methods correlated significantly, although this was closer for  $C_1$  than  $C_2$ , with noninvasive measures tending to overestimate.  $C_2$  was also reduced in hypertensives compared with age-matched controls, although the use of tonometry appeared to be less sensitive in detecting this difference than was previously reported in an invasive study.<sup>93</sup>

Assessment of arterial compliance by using DPCA has been applied to a number of at-risk populations. Using both brachial artery waveforms obtained invasively and radial artery waveforms obtained noninvasively with tonometry, increased age was associated with reduced large and small artery compliance,

whether assessed invasively or noninvasively.<sup>94</sup> Although the relationship between age and large artery compliance was similar however measured, the decline in small vessel compliance was greater when measured noninvasively. SBP was independently associated with reduced large artery compliance, but small artery compliance was not associated with any BP parameter. DPCA has been proposed as a sensitive marker of early vascular disease. In particular, reduced  $C_2$ , considered an early feature of impaired pulsatile arterial function, might be capable of identifying those at risk, providing an opportunity for early intervention. Although there were no differences in heart rate or BP, compared with matched controls,  $C_2$ , but not  $C_1$ , was decreased in patients with type II diabetes.<sup>95</sup> Analysis of brachial artery waveforms revealed that, compared with age-matched controls,  $C_2$  was reduced to a much greater extent than  $C_1$  in young hypertensives, whereas  $C_2$  was reduced to a similar degree in older hypertensives and controls.<sup>93</sup> Using radial artery waveforms obtained noninvasively, compared with matched healthy controls  $C_2$  was reduced in both hypertensives and postmenopausal women with CHD, whereas there were no differences in  $C_1$ .<sup>92</sup> Similarly, smoking was associated with impaired  $C_2$ , but not  $C_1$ .<sup>96</sup> Longitudinal studies investigating the value of DPCA are still to be performed.

The validity of DPCA has been subject to a number of criticisms. Referred to as distal, reflective, or oscillatory compliance, there is confusion as to precisely what  $C_2$  measures,<sup>82</sup> especially given that it does not refer to a well-defined arterial territory. As an overall measure of proximal and distal compliance of the entire circulation, it would, in theory, be expected that there would be no significant variation in the calculated values with the site of measurement. However, an invasive study performed in dogs found that there was little or no correlation between compliance values obtained at the ascending and terminal aorta.<sup>97</sup> There was also poor agreement between the two sites for the effect of vasoactive agents on compliance. In humans, values for  $C_1$  and  $C_2$  measured at the radial artery were not significantly correlated with those measured at the posterior tibial artery.<sup>98</sup> Rather than a reliable measure of overall proximal and distal compliance, it is likely that regional circulatory properties, such as arterial length, number of reflection sites and stiffness of individual arteries, have significant influence on these measures. Furthermore, despite good quality tonometry recordings, application of the model used in the technique yielded uninterpretable values for compliance in some subjects.<sup>98</sup> For example, where negative compliance values were obtained further analysis revealed wave peaks late in diastole, although the origin of these was uncertain. These findings currently cast doubts over the reliability of this methodology in accurately determining arterial compliance variables.

#### *Digital Volume Pulse (DVP)*

Digital arterial pressure and volume waveforms are also readily measurable. The digital pressure pulse closely mirrors the radial pressure pulse. The DVP, measured by using photoplethysmography, has a different contour, but can predict both digital and radial pressure pulses through a generalized transfer function that appears to be appropriate for use in healthy subjects, hypertensives and after nitroglycerine administration.<sup>99</sup> The DVP is characterized by an inflection

**TABLE 2. Comparison of Major Methods Used in the Noninvasive Assessment of Arterial Stiffness With Regard to Their Potential For Wider Clinical Use**

	PWV*	Arterial Ultrasonography	MRI	SPCA	Carotid Alx	DPCA
Ease of use	++	+	+	+++	+++	+++
Quality of validation	++	++	+++	++	++	+
Affordability	+++	++	+	+++	+++	+++
Freedom from operator bias	++	+	+++	++	++	++
Evidence of prognostic value	+++	++	+	+	++	+
Endothelial function testing†	+	+++	+	+++	+++	++

\*Excluding MRI

†Potential for practical application to the noninvasive assessment of endothelial function

Comparison of the major methods used in the noninvasive assessment of arterial stiffness with regard to their potential for wider clinical use. Carotid Alx, directly measured noninvasively using applanation tonometry, is considered separately to SPCA, which uses a generalized transfer function to derive central aortic Alx.

point, or notch, and the height of this has been suggested as a measure of peripheral pressure wave reflection.<sup>100</sup> However, although inexpensive and easy to use, there is, to date, little experience in the use of the DVP for the assessment of arterial stiffness. Further work to validate the technique, as well as establishing its precise relationship with the central arterial waveform, needs to be done.

### Comparison of the Different Methodologies

The relationship between different measures of arterial stiffness has been assessed in a number of studies. Using DPCA,  $C_1$  was closely correlated to both the ratio of stroke volume (SV; determined non-invasively) to PP (SV/PP has been proposed as a measure of total arterial compliance,<sup>101</sup> and aortic distensibility measured by MRI, whereas  $C_2$  correlated with SV/PP, but not aortic distensibility.<sup>102</sup> In a further study the correlation between stiffness parameters obtained by using SPCA, DPCA, and a third method that uses cuff plethysmography to measure brachial artery compliance was investigated.<sup>103</sup> Overall, different measures of compliance were only weakly correlated among themselves and with BP, although the cardiac time-tension index, the integral of the central pulse waveform from its beginning to the dichrotic notch, which is considered a measure of cardiac load,<sup>104</sup> was reasonably correlated with SBP and MAP. SPCA and DPCA have also been compared in a further study.<sup>105</sup>  $C_2$  was significantly and inversely correlated with AIx, providing support for the notion that  $C_2$  is determined, at least in part, by arterial wave reflections. The authors also reported inferior reproducibility in the measurement of  $C_2$  compared with AIx, although this finding has been challenged.<sup>106</sup> Invasive measures of aortic and radial artery waveforms in patients with CHD and hypertension have been used to investigate the relationship between AIx and  $C_2$ .<sup>82</sup> The two parameters were significantly, but not strongly, correlated. Thus,  $C_2$  reflected, at least in part, hemodynamic changes affecting central aortic pressure. AIx was more sensitive to the hemodynamic effects of glyceryl trinitrate (GTN) than  $C_2$ .

As has previously been argued,<sup>107</sup> there is a need for a simple, reliable, noninvasive method of detecting early disturbances in arterial stiffness at a time when therapeutic intervention can be

most beneficial. Currently, none of the methodologies available are yet suitable for use in widespread clinical practice. However, internationally recognized standards are being developed. In 2000 the First Consensus Conference on Arterial Stiffness was held in Paris and articles focusing on validation and reproducibility,<sup>108</sup> recommended procedures<sup>109</sup> and reference values<sup>48</sup> for the different methodologies have recently been published. In addition, regular workshops on the structure and function of large arteries have been held, which include discussion of methodology.<sup>110</sup> A summary of our views on the relative strengths and weaknesses of the major technologies is given in Table 2. Arterial waveform analysis by using tonometry of the radial artery requires minimal training and can be rapidly measured, such that it could easily be incorporated into an office visit as part of a clinical trial. In contrast, PWV and ultrasonography are more time consuming and ultrasonography in particular requires substantial training and is likely to require dedicated staff. The limitations of DPCA make it less likely that it will emerge as the preferred method of arterial waveform analysis. With regard to prognostic value, currently the most characterized of the measured parameters is aortic PWV. However, data on the prognostic value of AIx are emerging and in some cases suggest it is more powerful than PWV.<sup>90</sup> The results of ongoing studies are eagerly awaited.

### Effects of Cardiovascular Drugs on Arterial Stiffness

As arterial stiffness has become established as a cardiovascular risk factor in its own right, it has also emerged as a potential target for intervention. Indeed, it is conceivable that reduction of arterial stiffness may become a major primary goal of treatment in particular patients at risk of cardiovascular disease. However, for this situation to arise increased arterial stiffness will not only have to be established as an important independent cardiovascular risk factor, but also reducing arterial stiffness will need to be shown to reduce risk, independent of other effects of treatment. In the first instance, establishing whether currently used cardiovascular drugs potentially exert their clinical benefit through improvements in arterial elasticity may lead to more appropriate targeting of these treatments. However, many of these agents also lower BP and this effect must be differentiated from any

intrinsic effects, either structural or functional, on arterial wall stiffness.

The effects of organic nitrates, especially GTN, on the central aortic waveform have been well characterized. GTN effectively reduces central measures of AIx, SBP and PP but has little or no effect on peripheral arterial resistance, peripheral BP, or aortic PWV.<sup>111–113</sup> The greater effect of GTN on central than peripheral arteries is particularly evident at lower doses and probably the result of reduced peripheral wave reflection due to dilatation of muscular conduit arteries.<sup>114</sup> Indeed, direct measurement of brachial artery compliance with ultrasound has demonstrated improvements with GTN that are independent of distending pressure.<sup>22</sup> Other than when combined with hydralazine for the treatment of heart failure,<sup>115</sup> organic nitrates are not known to improve clinically important endpoints such as mortality and vascular events. The likely explanation for this is that their use is associated with increased production of superoxide anions, endothelial dysfunction and the development of tolerance to their effects.<sup>116</sup> However, the potential clinical benefits of specifically targeting organic nitrate therapy to patients with increased arterial stiffness have not been fully investigated.

Both calcium channel blockers (CCBs) and ACE inhibitors also appear to have beneficial effects on arterial elasticity independent of effects on distending pressure. For example, favorable effects on stiffness have been recorded with nitrendipine in patients with ESRF<sup>117</sup> and hypertension,<sup>118</sup> and with a number of ACE inhibitors in hypertension.<sup>119–121</sup> The degree to which ACE inhibition reduces arterial stiffness may be, at least in part, genetically determined. Polymorphism of the angiotensin II type-1 receptor gene influences the extent to which perindopril reduces both BP and PWV independently of BP.<sup>122</sup> Polymorphic variation in this gene also influenced the effect of nitrendipine on PWV, although there was no influence on the BP response.<sup>122</sup> Angiotensin II receptor antagonists have similar effects to ACE inhibitors on arterial stiffness in hypertension<sup>123</sup> and congestive heart failure (CHF),<sup>124</sup> although the latter study did not use BP at the artery under investigation when calculating distensibility. The dual ACE and neutral endopeptidase inhibitor omapatrilat was more effective than enalapril in reducing proximal aortic stiffness in hypertensives withdrawn from other treatment.<sup>125</sup>

A number of studies have compared the effects on arterial stiffness of ACE inhibitors and CCBs. In ESRF treatment for 1 year with perindopril or nitrendipine similarly reduced BP and more effectively reduced carotid than brachial pressure, restoring physiological peripheral amplification of SBP and PP.<sup>126</sup> Both similarly reduced PWV and carotid AIx, although only perindopril reduced left ventricular hypertrophy, suggesting additional modification by perindopril of factors other than left ventricular afterload. In hypertension, 8 weeks of treatment with lisinopril more effectively reduced PWV than nifedipine<sup>127</sup> and, after 20 weeks of treatment, derapril improved carotid distensibility whereas manidipine did not.<sup>128</sup> Using invasively-determined pressure-diameter curves, the acute administration of diltiazem improved aortic elasticity through, at least in part, effects on the intrinsic elastic properties of its wall.<sup>63</sup> In contrast, acute administration of enalapril had no effect on the intrinsic elastic properties of the aorta.<sup>61</sup>

The  $\beta$ -adrenoceptor blocker atenolol was one of the antihypertensives used in the SHEP study,<sup>9</sup> which demonstrated the

benefits of treating ISH. However, although  $\beta$ -blockers may reduce large artery stiffness, their effects on peripheral wave reflection and the central arterial waveform are less favorable, highlighting a potential limitation in the use of SPCA both as a marker of prognosis and of treatment benefit. After 6 months of treatment in hypertensives, atenolol was as effective as the ACE inhibitor cilazapril in increasing aortic elasticity.<sup>129</sup> However, atenolol was less effective than either fosinopril after 8 weeks of treatment<sup>130</sup> or perindopril after 1 month of treatment<sup>131</sup> in lowering directly measured carotid AIx. In a further study, treatment for 1 year with atenolol or perindopril/indapamide similarly reduced aortic PWV but only the ACE inhibitor/diuretic combination reduced carotid AIx.<sup>132</sup> As a confounding variable heart rate reduction with atenolol largely accounts for these differences, although functional or structural changes in the peripheral circulation might also affect the pattern of wave reflection.

There are conflicting data regarding the effects of diuretics on arterial wall stiffness. For example, despite reducing BP, neither indapamide nor canrenoate changed PWV.<sup>133</sup> However, in hypertension, there was a comparable improvement in arterial stiffness following treatment with perindopril or combined hydrochlorothiazide and amiloride in one study,<sup>134</sup> although perindopril was more effective than the diuretic combination in reducing arterial stiffness in a further study.<sup>135</sup> In the latter study arterial properties returned to baseline within 7 weeks, perhaps suggesting that the beneficial changes were functional, rather than structural. The CCB felodipine more effectively improved brachial artery compliance than hydrochlorothiazide, although the effects on MAP were slightly greater with felodipine.<sup>136</sup>

The effect of cholesterol lowering with 3-hydroxy-3-methyl coenzyme A reductase inhibitors (statins) on arterial stiffness has also been investigated. In familial hypercholesterolemia improvements in elasticity have been demonstrated in the common femoral but not the carotid artery after 1 year of simvastatin or atorvastatin,<sup>137</sup> in the aorta after 13 months of cholesterol-lowering treatment that included pravastatin,<sup>138</sup> and in the radial artery after 2 years but not 6 months of simvastatin.<sup>139</sup> In nonfamilial hypercholesterolemia, simvastatin improved femoral-posterior tibial but not aortofemoral PWV, although treatment was only given for 4 weeks.<sup>140</sup> In patients with ISH and relatively normal plasma cholesterol concentrations, not taking antihypertensive medication, atorvastatin for 3 months reduced systemic arterial compliance, assessed noninvasively.<sup>141</sup> SBP was also reduced by atorvastatin in this study. Although there was a reduction in peripheral resistance and MAP, these changes were small and it is likely that the reduction in SBP was secondary to reduced arterial stiffness. Using DPCA a reduction in small artery compliance after 4 weeks of atorvastatin has also been reported, although this was an open study without a placebo control.<sup>142</sup>

Drugs may improve the stiffness of the arterial wall through either functional or structural mechanisms. Although there are a number of approaches to investigating these mechanisms, such as the use of animal models, some insight can be gained from the noninvasive assessment of arterial stiffness. For example, the time on treatment required for benefit to occur might be informative. Although ACE inhibitors have no effect on the intrinsic stiffness of the aorta when given acutely<sup>61</sup> there is



abundant evidence that regular ACE inhibition over several months or more reduces arterial stiffness. Structural changes to the arterial wall would be expected to accrue over time and may, therefore, explain these differences between acute and chronic effects. The changes in arterial elasticity that occur following cholesterol lowering with statins also appear to be related to time on treatment, suggesting that structural changes occur. In contrast, CCBs reduce stiffness with regular treatment, but also do so acutely.<sup>61</sup> Thus, CCBs appear to improve elastic properties in a functional manner, although later structural changes cannot be excluded. It should be noted that structural changes might not be the only explanation for improvement in elasticity related to time on treatment, because interventions that improve endothelial function, thus reducing stiffness in a functional manner, may take time to work.

### Endothelial Function

There are now a number of published studies demonstrating the independent prognostic value of endothelial dysfunction.<sup>143–146</sup> Both endothelial dysfunction and increased arterial stiffness commonly coexist in patients at increased risk of cardiovascular disease, for example in diabetes<sup>87,147</sup> and in smokers.<sup>148,149</sup> Indeed, some studies in children have directly related increased stiffness with impaired endothelial function, for example in low birth weight,<sup>150</sup> familial hypercholesterolemia,<sup>151</sup> and severe obesity.<sup>152</sup> These observations lead to the hypothesis that cardiovascular risk factors may exert their detrimental effects on arterial stiffness through endothelial dysfunction.

Evidence from both animal<sup>153,154</sup> and human studies suggests that the endothelium is an important regulator of arterial stiffness, both functionally and structurally. Inhibition of basal nitric oxide (NO) production in the endothelium with L-monomethyl-*N*<sup>G</sup>-arginine (L-NMMA) increases iliac PWV in sheep<sup>21</sup> and, in humans, increases AIx<sup>155</sup> and brachial artery stiffness.<sup>20</sup> The reduction in arterial stiffness with acetylcholine, an endothelium-dependent vasodilator, is also inhibited by L-NMMA in large arteries.<sup>21</sup> However, in one human study, although acetylcholine increased brachial artery elasticity, L-NMMA paradoxically increased compliance of the artery.<sup>156</sup> Using DPCA in healthy volunteers, inhibition of endogenous NO synthesis increased BP and decreased small artery compliance, but had no effect on large artery compliance.<sup>157</sup> These changes were reversed with L- but not D-arginine. The importance of endothelium-derived NO to the structural integrity of the arterial wall is emphasized by a study in which disruption of the endothelial NO synthase gene in mice promoted abnormal arterial remodeling.<sup>158</sup> In healthy subjects, increased vessel wall shear stress (resulting from increased flow that occurs with distal vasodilatation secondary to, for example, reactive hyperemia) leads to endothelium-dependent arterial dilatation. The same stimulus also increases local arterial distensibility.<sup>159</sup> At the brachial artery both endothelial function and shear stress-stimulated increased distensibility are impaired in patients with CHF. In contrast, the increase in distensibility that occurred with endothelium-independent stimuli was retained in patients with CHF.<sup>159</sup> Furthermore, acetylcholine reduced local PWV of the right common iliac artery in healthy subjects but not in those with CHF.

A number of interventions that reduce arterial stiffness also improve endothelial function, particularly ACE inhibitors<sup>160,161</sup> and statins.<sup>162,163</sup> To date, there have been few studies specifically investigating the relationship between these two markers of vascular function after treatment. However, in CHF patients 2 months treatment with perindopril improves both flow-dependent dilatation and flow-dependent change in distensibility of the radial artery.<sup>164</sup> Patients with growth hormone deficiency, who are at increased risk of vascular disease, have impaired endothelial function and increased AIx compared with controls.<sup>165</sup> Indeed, endothelial dysfunction, assessed as flow-mediated dilatation of the brachial artery, independently predicted AIx in this population. Replacement of growth hormone resulted in improvement of both endothelial function and AIx, without changing BP.<sup>165</sup> Further studies are required to fully define the link between endothelial function and arterial stiffness. Although most studies suggest that the endothelium regulates stiffness, impaired elastic function itself might have adverse effects on endothelial function, and future work needs to address this issue. Investigation of the relationship between arterial stiffness and endothelial function, as well as of the clinical value of assessment of endothelial function, will be aided by the recent development of a noninvasive methodology that measures endothelial function by using SPCA. The  $\beta$ 2-adrenergic receptor agonist albuterol lowers both the inflection point of the DVP,<sup>100</sup> and AIx measured by SPCA.<sup>166</sup> These actions of albuterol are mediated, at least in part, through the NO pathway. Furthermore, in patients with hypercholesterolemia, known to have impaired endothelial function, the effect of albuterol on AIx was blunted, and this correlated well with impaired endothelial function measured as acetylcholine-induced vasodilatation in the forearm by using strain gauge plethysmography. In contrast to other methodologies, assessment of endothelial function with SPCA, and potentially also by using the DVP, can readily be applied to large numbers of subjects in clinical trials.

### The Future

A number of technologies can measure arterial stiffness noninvasively. The relatively low cost, ease of use, and acceptability to patients of many of these technologies has resulted in a rapid expansion of work in this field, although the full clinical impact of these measurements is not yet clear. Where possible, therefore, these technologies should now be incorporated into longitudinal studies, so that the prognostic value, relative to established predictors of risk, of the various parameters can be fully defined. Although the prognostic value of some technologies, especially PWV, has been investigated, these studies have generally been small and have been performed in a limited number of at-risk groups. Larger studies, in a greater number of at-risk populations, are required. This knowledge will facilitate greater confidence that the effects of drugs and other interventions on these parameters may truly be relevant to important clinical outcomes. It is of paramount importance that studies are standardized<sup>109</sup> and take into account known confounding factors. Noninvasive technologies should also be used to more fully characterize the effects of existing drugs on arterial stiffness, including quantifying the degree to which their beneficial effects are the result of improvements in the elastic properties of the arterial wall. Furthermore, these methodologies should also

provide a means of unraveling the influence of genetic factors on both the development of stiffness and its response to treatment.

There are a number of novel approaches to treatment that might prove particularly valuable in reducing arterial stiffness and its clinical consequences. For example, breaking advanced glycation end-product crosslinks, alterations in matrix proteins that accumulate in arterial wall elastin and collagen and increase wall stiffness, has recently been shown to improve arterial compliance in elderly humans.<sup>167</sup> The provision of exogenous NO to the arterial wall may also be of benefit, such as with novel NO donors that do not undergo tolerance.<sup>168</sup> Alternatively, the activity of the vascular NO-cGMP pathway might be enhanced with inhibitors of phosphodiesterase-5 or stimulators of guanylate cyclase.

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