Arterial Stiffness: Going a Step Beyond

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Interest in arterial stiffness has been fueled by the scientific and clinical implications of its “vicious cycle” relationship with aging and systolic blood pressure. In physical terms, stiffness is the slope of the relationship between an artery’s distending pressure and its cross-sectional area or volume. Pulse wave velocity (PWV), the most common arterial stiffness indicator, is usually measured by the foot-to-foot time and distance method and is proportional to [stiffness × area (or volume)]1/2 at a given pressure. Its intrinsic pressure dependency and other flaws in current PWV methods limit its utility. In contrast, the arterial stiffness–arterial pressure relationship is near-linear, with a slope β, the exponent of the curvilinear arterial pressure–arterial volume relationship. The concept of arterial stiffening is related to β and describes a more functionally relevant aspect of arterial behavior: the change in stiffness for a given change in pressure. Arterial stiffening can be estimated from the variability of within-individual BP measurements (24-h ambulatory, home BP, or BP measured at different arm heights) and can be expressed as the pulse stiffening ratio (PSR) = \( \beta\frac{\text{diastolic stiffness}}{\text{diastolic stiffness}} \) or the ambulatory arterial stiffness index (AASI or its symmetric form, sAASI). High arterial stiffness (PWV) and stiffening (\( \beta \), stiffness index, cardio-ankle vascular index, AASI, and PSR) are associated with increased cardiovascular disease risk, but it remains unclear whether these indicators are useful in improving medical care quality; the standard of care remains stringent BP control.

Keywords: arterial stiffening; arterial stiffness; blood pressure; blood vessels; biomarkers; hypertension; methods.

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Aging and increasing systolic blood pressure (BP) are linked together by increasing arterial stiffness, defined loosely as the resistance of the arterial wall to expansion by an increment in volume. Arterial stiffness is the tangent slope of the nonlinear relationship between arterial pressure and arterial volume (or cross-sectional area). Pulse wave velocity (PWV), the most common surrogate for arterial stiffness, is commonly misinterpreted as a static indicator of arterial wall properties. In reality, stiffness varies with any change in distending pressure or input volume, including each cardiac systole. We describe this dynamic property as “arterial stiffening,” which is not fully predicted by knowing the diastolic stiffness of the artery. The goal of this work is to provide a conceptual basis for interested clinicians and researchers to interpret existing literature and to anticipate future developments in the study of arterial function. We also include editorial commentary on the scientific and clinical use of available arterial function indicators.

PATHOGENESIS AND IMPACT OF STIFF ARTERIES AND PRESSURE-RELATED STIFFENING

BP configuration changes with aging. Until middle age, systolic BP (SBP) and diastolic BP (DBP) increase in tandem but thereafter DBP declines while SBP continues to increase, leading to a widened pulse pressure (PP, SBP minus DBP) and often to systolic hypertension.1,2 This age-related SBP-DBP divergence also signals a change in the pathophysiology of hypertension, where increasing arterial stiffness is progressively superimposed upon the basic hemodynamic profile of hypertension: the product of inappropriately high cardiac output and inappropriately high systemic vascular resistance.3-7 In older individuals, both the increase in systolic BP and the decrease in diastolic BP increase cardiovascular risk. Histopathologic changes in the arterial wall that underlie these hemodynamic patterns include deterioration of the elastin network, vascular smooth muscle hypertrophy, and increased medial and adventitial collagen deposition.8,9 This diffuse process of adventitial and medial fibrocalcific change or “pure arteriosclerosis” is largely independent of atherogenesis, the atherothrombotic occlusive process caused by endothelial and medial deposition of oxidized cholesterol, focal endothelial inflammation/ulceration, plaque remodeling, and thromboembolism.4 From a mechanical perspective, aging is associated with reduced effectiveness of the aortic “Windkessel,” the arterial volume reservoir that dampens cardiac pulsation. Loss of elasticity causes increased SBP, reduced diastolic flow and DBP, and widening of PP, the cardinal clinical sign of increased arterial stiffness.10-12 With aging, the aorta and major arteries lose elasticity, but also undergo compensatory dilatation,5,13-16 probably caused by the lifetime burden of cyclic pulsatile pressure stress. This dilation helps maintain total arterial compliance (the Windkessel function) by substituting increased arterial volume (or cross-sectional area)
for the “lost” wall elasticity. The effectiveness of this compensation is limited by the greater relative arterial stiffening during systole in the larger stiffer artery, which also reduces arterial volume expansion at any given PP.

Arterial stiffness is often discussed as if it were a static property of a given artery (or region) but this is not the case. Arterial wall characteristics directly affect arterial stiffness but the term “stiffness” is intrinsically dynamic in that it also depends on arterial size and distending pressure. Thus, arterial stiffness is not constant within an individual, not even within a single cardiac cycle. The change in stiffness that results from a given increment in distending pressure is termed “arterial stiffening.” This property has been demonstrated in many animals and is an important clue to the dynamic process of arterial accommodation to physiologic and pathologic changes in the arterial tree. The arterial stiffening concept underlies many of the newer techniques to assess optimal and suboptimal arterial function that are discussed in subsequent sections.

One of the most significant of the current debates is whether increased arterial stiffness precedes systolic hypertension, or perhaps whether the relationship is best viewed as a vicious cycle where each is both cause and effect. It would seem that the vicious cycle concept is a very good explanation for the observed age-related pathophysiologic changes. For example, in chronic hypertension, when brachial BP is normalized by external compression, the high brachial artery stiffness is also normalized. However, older normotensives have higher arterial stiffness than young normotensives but also have higher SBP and PP for the same mean arterial pressure. As PP increases with age and hypertension, diverse organ-related changes also occur, such as increased cardiac afterload and left ventricular hypertrophy. Accompanying microcirculatory rarefaction and increased microcirculatory pulsatility reduce the efficiency of oxygen and nutrient delivery and promote glomerulosclerosis and chronic kidney disease progression as well as cerebral microvascular disease and cognitive impairment. This integrated model of age-systolic BP–stiffness–target organ damage is not fully proven but is consistent with many observations.

**ARTERIAL STIFFNESS**

**Basic concepts: Age and arterial caliber, pressure, and stiffness**

A number of important arterial properties can be derived from the curvilinear relationship between arterial pressure and luminal cross-sectional area (or arterial volume for a given segment) as shown in Figure 1 for normal and clinically elevated BP.

\[
\text{Pressure} = \alpha + \gamma \exp(\beta \cdot \text{Area})
\]

where \(\alpha\), \(\beta\), and \(\gamma\) are pressure-independent constants. A full discussion of the unique aspects of these constants is beyond the scope of this paper, but in general, \(\alpha\) is related to intrinsic properties of an artery to remain patent at very low pressures and \(\gamma\) is a scaling factor for the \(\gamma\)-intercept. Higher \(\beta\) signifies greater stiffening (a greater pressure increase for a given increment in arterial volume). Equation (1) has been used for fitting similar data with \(\alpha\) and without \(\gamma\) and for describing pressure–volume relationships in the left ventricle.

An important principle is that arterial distending pressure and arterial caliber combine with arterial wall characteristics to determine arterial stiffness; another component, blood density, is usually ignored. Caliber refers to the cross-sectional area of the artery but “volume” and area are often interchangeable (i.e., if area equals volume/length for an arterial segment). Figure 1 defines the pressure–area relationship for two groups of individuals: a younger group with lower BP and an older group with higher BP; aortic caliber is also greater in the older group, as observed by Hallock and Benson. To construct this figure, aortic size data were taken from autopsy studies in which five age-groups were represented; data from two of these groups are embedded in Figure 1. BP values corresponding to these age-groups were taken from more recent US population data. It could be argued that in vivo aortic caliber might have been more appropriate but results would have been similar to those depicted. Aortic size data and the corresponding BP data were then fit to equation (1). The most clinically relevant BP range is above 75 mm Hg, where both curves can be described remarkably well. The effect of aging (and increased vessel caliber) on arterial pressure–area curves is to cause a downward–rightward...
curve shift; note again that arterial cross-sectional area (and diameter) is greater in the older group, particularly at lower pressure levels. Below the operating pressure region, in which equation (1) is fully valid, the younger subject curve displays a transition at a point where the slope reaches a minimal value; this change in arterial behavior will be explained subsequently.

Stiffness (or more properly, elastance), the slope of the pressure vs. area (or volume) curve at any point, represents the ratio between a small incremental pressure change and the corresponding area (volume) change. Stiffness becomes “incremental elastic modulus” if the area (volume) change is expressed relatively.\(^ {30}\) Stiffness is the reciprocal of arterial compliance.\(^ {31}\) A highly compliant artery can store more blood with a lesser increase in pressure than one that is stiffer but a larger artery will have greater compliance than a smaller one if the arterial wall composition is similar. It can be seen from Figure 1 that in the normal and higher blood pressure range, stiffness increases directly with pressure; it also increases during each systole and decreases during each diastole. The concave part of the pressure–area curves shown in Figure 1 and the resulting changes in pressure-dependent stiffness stem from the structure, organization, and behavior of the constituent arterial wall components (elastin, collagen, and smooth muscle) and their interaction with arterial caliber, all of which change with age.\(^ {32,33}\) Thus, different arteries with different sizes and proportions of wall constituents may display different relationships between stiffness and pressure.

Pulse wave velocity

The oldest and simplest indicator of arterial stiffness is the velocity of the arterial pressure wave (PWV). According to the formula derived over 100 years ago by Moens and Korteweg and modified later by Bramwell and Hill,\(^ {34}\) PWV can be written as:

\[
\text{PWV} = k \cdot \left( \frac{\text{Incremental bulk modulus}}{\rho} \right)^{\frac{1}{2}}
\]  

(2a)

where \(k\) is a constant and \(\rho\) is the blood density. The original Bramwell–Hill equation can be written as:

\[
\text{PWV (m/s)} = 0.357 \cdot \left[ V \cdot \left( \frac{dP}{dV} \right) \right]^{\frac{1}{2}}
\]  

(2b)

where \(dP/dV\) is stiffness, i.e., the tangent slope of the pressure–volume curve (Figure 1). Equations (2a) and (2b) require inclusion of a reference (basal or initial) cross-sectional area (or volume), which is largely its diastolic value. Assessment of arterial stiffness has been both direct and indirect but for clinical purposes, only the indirect techniques are relevant.

“Foot-to-foot method.” The standard clinical method for PWV is to measure the distance between two distal arterial sites and then to divide this distance by the difference in pulse arrival times. Because of distortion of the systolic peak by differential wave propagation speeds,\(^ {35–37}\) the “foot-to-foot” method is used for the determination of pulse arrival times.\(^ {38}\) The “foot-to-foot” method is more closely related to diastolic than systolic pressure,\(^ {39}\) i.e., it predominantly reflects diastolic stiffness but may also contain a component of systolic stiffness. Of substantial concern is the routine practice of ignoring the baseline (diastolic) arterial cross-sectional area that confounds the interpretation of compliance (change in volume/change in pressure) and its reciprocal, stiffness. Instead, it would be more appropriate to consider arterial distensibility (\(dV/VdP\)) or its reciprocal, the elastic modulus (elastance). This is especially true because a stiffer artery could simply be smaller (reduced volume or area) or it could have altered wall composition (excess collagenous deposition). Finally, equation (2b) suggests that the pressure dependence of PWV is \textit{not} the same as that of stiffness because of the square root function; PWV\(^ {2}\) increases with pressure to a greater degree than stiffness does.

PWV, which is most commonly measured between the carotid and femoral arteries (cfPWV), has been used in pathophysiological studies as well as large observational and follow-up investigations. Many investigators and some guidelines\(^ {40,41}\) favor routine clinical use of PWV as a cardiovascular disease risk assessment tool because of its proven association with cardiovascular and renal disease morbidity\(^ {42–46}\) and mortality\(^ {47–49}\) and the incremental improvement over standard cardiovascular disease risk factors that it may provide.\(^ {44,50–53}\) PWV is now widely available, reimbursable (United States) and is endorsed by the European Society of Hypertension and the European Society of Cardiology.\(^ {48}\) Consensus statements summarizing traditionally accepted concepts of arterial stiffness and PWV measurement provide an exhaustive bibliography for interested individuals.\(^ {52–54}\)

The authors of this review have a less positive opinion of standard PWV measurement due to the many questionable hidden assumptions, complex confounding relationships, and problems of measurement it represents. Nonstandardization of PWV methods makes it difficult to compare values between studies, although these methodological artifacts do not necessarily alter conclusions when a particular device is used in a single study that employs population stratification or follow-up strategies. Major confounders of PWV are treated inconsistently; PWV varies directly with age,\(^ {16,55–58}\) and arterial pressure\(^ {19,59,60}\) and inversely with heart rate.\(^ {61–64}\) Most studies ignore these interactions, which are not fully independent: older age is associated with greater stiffness (higher PWV) but also with lower diastolic pressure (reduced Windkessel function). The close relationship between age and PWV has led some investigators to suggest age normalization,\(^ {65}\) and a similar rationale could be offered for BP normalization. Better standardization is essential; at the very least, the dependence of PWV on BP dictates strict criteria for its measurement.\(^ {45,66,67}\)

There are other substantial theoretical and technical measurement problems. PWV is a lumped parameter that is an admixture of properties of different arteries (e.g., the aorta, carotid, and femoral arteries in cfPWV) that are
structurally dissimilar. The use of different measurement regions to represent the aorta (e.g. heart–femoral vs. brachial–ankle) is an intrinsic problem made worse by grossly incorrect height-based algorithms and inconsistencies in the anatomic landmarks chosen to represent arterial path length. For example, the most widely used method of PWV estimation, cfPWV (often mislabeled as "aortic PWV" using the Complior, Colin, or similar devices) has been calculated several different ways with dramatically different results. For a known mean catheter-based aortic PWV of 8.5 m/s, the corresponding carotid–femoral value was 11.5 m/s (35% higher) if arterial length was assumed as the uncorrected carotid–femoral distance (the most common approach). If a more appropriate distance correction was used (carotid–suprasternal notch distance subtracted from suprasternal notch–femoral distance), the PWV value was 8.7 m/s, similar to the invasive value. The problem is even worse for distal measurement sites; brachial–ankle PWV, although correlated with central measurements, exceeds true aortic PWV by at least 50%. Because of these vagaries, newer PWV techniques continue to arise. One method estimates heart–femoral PWV (Colin VP 1000/2000) from the timing of aortic valve closure (by phonocardiography and electrocardiography) and the foot of the femoral pulse wave measured by arterial tonometry. The Colin device also measures standard cfPWV and brachial–ankle PWV.

Systolic stiffness. Systolic PWV is always greater than diastolic PWV because of the pressure dependence of PWV. However, systolic PWV is more likely to be of clinical significance than diastolic PWV because it represents the most stretched state of the artery. This principle is embedded in the concept of arterial stiffening as will be discussed in detail in the next section. One device (MobilOGraph with ARC Solver) uses 24-h ambulatory oscillimetry with pulse wave analysis to create a proprietary transfer function–derived central pressure waveform and a corresponding PWV (said by the manufacturer to depend on age, central BP, and aortic impedance). Aortic PWV values by this method are much closer to invasively determined aortic PWV but other information suggests that the method tracks systolic rather than diastolic PWV. In our studies, about 90% of the intrindividual variation in PWV throughout the day can be explained by the corresponding variation in systolic BP, while 92% of the interindividual variation in PWV can be explained by age (85%) and systolic BP (7%). In other studies, end-systolic PWV (BP measured at the dicrotic notch) has a much stronger association with PP and age than does standard (diastolic) PWV.

Pulse pressure amplification and AIx. Pulse wave analysis allows estimation of other central BP and other potential indicators of arterial function. Another phenomenon related to PWV is pulse pressure amplification (higher distal than central PP and systolic BP), which is at least part due to the distortion of the systolic pulse waveform by variations in PWV during systole. High pulse pressure amplification can be caused by anatomical differences in artery caliber even if the wall elastic properties are normal; in smaller peripheral arteries that taper, there is a progressive increase in systolic BP, impedance and PWV even if the wall composition is perfectly normal. Historically, late systolic pressure augmentation (augmentation index (AIx)) was used as an indirect index of arterial stiffness but more recent thinking suggests that this practice should be reconsidered. AIx and PWV both tend to be high in older individuals and therefore are often correlated; this does not mean, however, that AIx is a reliable indicator of arterial stiffness. This misunderstanding was largely related to outdated concepts of wave reflection theory which held that decreased pulse transit time in stiff arteries (high PWV) caused the backward arterial pressure wave to appear “prematurely” in late systole, where it caused enhanced summation with the forward pressure wave. However, several investigators have now refuted this model of pressure wave reflection; the return wave can be found in all individuals in late systole. AIx is more dependent on the reflection coefficient, which in turn is influenced heavily by distal vascular resistance.

ARTERIAL STIFFENING

Arterial stiffness indicators provide limited predictive information about the dynamic behavior of arteries over the range of physiologic and pathophysiologic changes observed in the population. Although PWV varies with aging and disease, it fails to capture the dynamic essence of arterial mechanics. As depicted in Figure 1, full appreciation of the implications of the nonlinear pressure–area relationship requires a more inclusive approach.

Stiffness–pressure relationship

The nonlinear concave form of the pressure–area curves shown in Figure 1 and the variations with aging and disease stem from the structure and organization of the wall components: elastin, collagen, and smooth muscle and their dissimilar pressure and size-dependent interactions. Arterial stiffness is the slope of the pressure–area (or volume) curve, but arterial stiffening is the nearly constant slope of the arterial stiffness–pressure curve (β) over the usual operating range of pressures in man. Stiffening also can be described as the change in stiffness that accompanies a given pressure increment. Figure 2 is derived directly from Figure 1; in the usual operating range, from equation (1):

\[
\text{Stiffness} = \beta \cdot (P - \alpha)
\]

\[
\beta = \frac{\ln[(SBP - \alpha)/(DBP - \alpha)]}{\text{Pulse area}}
\]

The dimensions of β are 1/area (or 1/volume). Current clinical estimation of β involves modified forms of equation (4). Differences in β between individuals strongly depend on arterial wall characteristics; zero β corresponds to a purely elastic artery, i.e., stiffness is a pressure-independent

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constant, while higher $\beta$ implies stiffening. Conceptually, stiffness and stiffening are independent measures; arteries may display high or low stiffness independent of pressure, while others may demonstrate a close relationship of stiffness and stiffening in part due to alterations in elastin and collagen content.

Figure 2 also demonstrates that at low pressures (and minimum stiffness), stiffening (defined by the tangent slope) can be low, zero, or even negative (see shaded area for the younger group). These phenomena reflect different structure–function characteristics that vary with arterial pressure and age and arterial wall composition. The pressure at the point of minimum stiffness (maximum compliance) represents a complex transition between a "normally distended" vs. "collapsed" (more properly "buckled") configuration of the artery. Buckling is a term that refers to a conformational shift in the vessel (e.g. convex to crescentic) where there is a large reduction in the lumen area for a relatively small pressure reduction. This shift is manifested by the disappearance of the buckling phenomenon and appearance of an older type artery that never collapses fully, instead remaining ovoid with a finite diameter and stiffness even at zero pressure. The younger type curve is more common in the thoracic and abdominal aorta, while the older type is more common in peripheral conduit arteries, including the brachial and radial arteries. The buckling aspect in pressure–area relationships has been used to model ex vivo and in vivo pressure dependence of arterial compliance. Finally, if the linear stiffness–pressure relationship (equation (4)) observed at higher pressures is extrapolated back to zero stiffness (see Figure 2), the line crosses the pressure axis at a value $\alpha$ of approximately 40–55 mm Hg. The same $\alpha$ range was obtained by Cox using data from six different types of arteries. Our interpretation of this information is that $\alpha$ is an estimate of "collapsibility" of an artery, which in turn is related to its structural characteristics (e.g., collagen content) and to its stiffness. These and other aspects of low pressure arterial behavior deserve further investigation.

**Clinical estimation of $\beta$**

**Stiffness index.** Stiffness index (SI) is a dimensionless index defined as follows:

$$SI = \frac{\ln(SBP/DBP)}{(Pulsediameter)/(Diastolicdiameter)}$$

Equation (5) can be obtained from equation (4) by ignoring $\alpha$, thus expressing cross-sectional area relative to its diastolic value, and approximating the relative pulse area (i.e., [systolic minus diastolic area]/[diastolic area]) as twice the relative pulse diameter. This approximation makes SI roughly equal to $2\beta$[diastolic area]. Systolic and diastolic diameters can be measured noninvasively by echo tracking. Since the diastolic diameter varies with pressure, SI is clearly not a pressure-independent constant. The omission of $\alpha$ causes further severe limitations in its use; e.g., if $BP = 140/80$ mm Hg and $\alpha = 40$ mm Hg, $\beta$ in equation (4) is $\ln[(140 - 40)/(80 - 40)] = 0.92$, whereas SI in equation (5) is 0.56 (i.e., about 40% smaller). SI was originally suggested as an expression of arterial stiffness, and it does increase with age, hypertension, smoking and their interaction, and type 2 diabetes, and is an independent risk factor for recurrent acute coronary events.

**Cardio-ankle vascular index (CAVI).** This proprietary index has been claimed to be a pressure-independent estimate of $\beta_{6,7}$ and is derived from cuff $BP$ and standard PWV according to the following formula:

$$CAVI = a \cdot PWV^2 \cdot (2\rho/PP) \cdot \ln(SBP/DBP) + b$$

where $a$ and $b$ are adjustable constants. Derivation of equation (6) from equation (4) ignores $\alpha$ and replaces the required small pressure and volume changes in the Bramwell–Hill equation (equation (2b)) with central PP and pulse volume estimates that are not "small." This may explain the observed relationship between CAVI and SI. Equation (6) involves the unverified derivation of the constants $a$ and $b$. Clinical applications of...
CAVI were recently reviewed, and it has been claimed that this proprietary index yields prognostic information about cerebrovascular and coronary artery disease. Whether CAVI offers clinically useful incremental risk stratification or whether it is truly pressure independent remains to be proven.

**BP-derived arterial stiffening indicators**

Stiffening indicators can be derived from repeated BP measurements alone: pulse stiffening ratio (PSR) and two forms of ambulatory arterial stiffness index (AASI). They share a common purpose: providing easily measured, (largely) pressure-independent information with diagnostic and prognostic significance.

**Pulsatile stiffening ratio.** A simple and convenient way to express stiffening is the ratio [systolic stiffness]/[diastolic stiffness] or “PSR” (see Figure 2) as originally proposed by Gavish. Other names for PSR in past communications were: Sym-slope, s-slope, BP variability ratio (BPVR), S-D slope, and dSdD. Equation (3), PSR = (SBP − α)/(DBP − α), leads to the following predicted relationships:

\[
SBP = C + PSR \cdot DBP \quad (7a)
\]

\[
DBP = C' + (1/PSR) \cdot SBP \quad (7b)
\]

There is no a priori assumption that PSR, C, or C' are constants but the highly linear relationship between SBP and DBP in all individuals has been observed (Figure 3) for intra-arterial pressures, brachial 24-h ambulatory pressures, home BP monitoring, and gravitational-induced brachial BP change. This indicates that PSR is also pressure independent. When estimated from BP data using symmetric regression, PSR can be expressed as the ratio of SBP variation to DBP variation:

\[
PSR = \frac{SD(SBP)}{SD(DBP)} \quad (8)
\]

where SD is standard deviation. Equation (8) suggests that PSR can be determined theoretically from any type of consistently measured repeated BP values with sufficient range and variation. By definition, PSR = 1 for a purely elastic artery. A subject with greater variability of systolic than diastolic BP (PSR > 1) displays greater stiffening over the observed pressure range. The newer “gravitational method” for PSR determination also has promise (Figure 3). With a digital BP monitor and standard arm cuff, readings are taken at four different vertically displaced arm positions. The resulting 20 mm Hg of BP variation, the corresponding good SBP-DBP correlation (mean R = 0.94), and the minimal heart rate variation all contribute to reasonable reproducibility. In contrast to current belief, BP variation in response to changing arm cuff height cannot be explained solely by a hydrostatic effect. From our 24-h ambulatory monitoring data, mean PSR was 1.39 ± 0.33 (mean ± SD), range 0.59–3.5, mean error of determination 6%, mean SBP-DBP correlation of 0.76, and about 5% of the PSR values were <1. The negative stiffening in the low pressure range (as predicted in Figures 1 and 2) deserves further study.

There are other important implications of the highly linear relationship between SBP and DBP and the derivation of PSR. Stated differently, the model assumes that the linear SBP-DBP relationship is a physiological law and not just a statistical correlation. It predicts the observed exponential pressure–area relationship (Figure 1, equation (1)) and the associated linear stiffness–pressure relationship (Figure 2, equation (2)). Since PSR = exp (β·[Pulse area]), by combining equations (1) and (3), both PSR and β appear to be pressure independent. Pulse area (volume) and the Windkessel function (aortic volume reservoir) are also pressure independent. Several factors can alter PSR physiologically; Figure 4 shows that PSR varies inversely with heart rate, increasing more steeply for heart rates <70 bpm (along with DBP) and diastolic stiffness. Figure 4 also shows that PSR increases gradually at younger ages (<55 years) and more steeply in older individuals, consistent with our knowledge of arterial stiffness and stiffening. PSR is an independent predictor of all-cause mortality in the general population.

![Figure 3](https://academic.oup.com/ajh/article-abstract/29/11/1223/2408945) Linearity of systolic vs. diastolic BP. The slope is interpreted as an estimation for the PSR, see equation (7a) given as mean ± SD, using: (a) 24-hour ambulatory BP monitoring or (b) digital BP monitoring with “gravitational method” (see text). Data were reproduced with permission. BP = blood pressure; PSR = pulse stiffening ratio.
Finally, PSR = pulse dipping (higher in non-dippers).

AASI and sAASI. These indicators, like PSR, are derived from the observed linear relationship between SBP and DBP. AASI was originally defined as 1 – (diastolic-on-systolic slope) and was originally calculated using standard regression of 24-h ambulatory systolic and diastolic pressures. The formula for AASI is:

$$AASI = 1 - \frac{R}{PSR}$$  \hspace{1cm} (9)$$

where $R$ is the standard Pearson SBP-DBP correlation coefficient and PSR is given by equation (8). The dependence of AASI on $R$ (also observed experimentally) is a bias caused by the asymmetric characteristics of standard regression methodology that can be eliminated using symmetric regression technique, resulting in an $sAASI$:

$$sAASI = 1 - \frac{1}{PSR}$$  \hspace{1cm} (10)$$

Zero sAASI (but not AASI) corresponds to purely elastic artery. AASI can be easily converted to sAASI using the formula $sAASI = 1 - (1 - AASI)/R$, and the latter to PSR using the formula $1/(1 - sAASI)$. AASI and sAASI strongly correlate with PSR at least in part due to the common terms involved (Equations (9) and (10)). Reproducibility of AASI and sAASI using self-measured home BP values was somewhat lower than using automated 24-h monitoring. AASI is also substantially affected by physiologic variations in vascular resistance and heart rate (see Figure 4). PSR, sAASI, and especially AASI are also affected by nocturnal BP dipping (higher in non-dippers).

AASI and sAASI are primarily indicators of stiffening as supported by computer simulation. Due to the close mathematical relationship between PSR and sAASI, both would be expected to display similar diagnostic and prognostic significance; this is true for all-cause mortality. PSR and AASI (or sAASI) are positively correlated with high collagen/elastin ratio (in rats), and it should not be surprising that both may correlate with arterial stiffness indicators, at least in some instances. High sAASI is associated with microalbuminuria and reduced renal function. AASI predicts cardiovascular mortality and events, especially stroke but sAASI has stronger predictive power than AASI. Finally, using ambulatory BP measurements, PSR, sAASI, and AASI were reduced by 8 days of weekly treatment with device-guided breathing but were unaffected by 6-month potassium chloride-enriched diet or seasonal BP change suggesting that stiffening may be affected by certain therapeutic interventions. Alternatively, there may be a degree of “hidden” pressure dependency of these stiffening indicators that is not apparent in the concepts or formulas used to derive them.

Relevance and Applicability of Stiffness and Stiffening Indicators

A main goal of this work is to spark necessary discussion and debate about future needs and directions. From a scientific perspective, historical methods for arterial stiffness (mainly PWV) are limited in the information they provide. The first section of this review detailed a comprehensive framework for understanding arterial stiffness and its consequences. Subsequent discussion emphasized the intrinsic pressure dependence of arterial stiffness and the need for a more dynamic term (arterial stiffening) to describe clinically relevant, largely pressure-independent arterial behavior. There are now several approaches that yield information on arterial stiffness and stiffening. In describing the dynamic relationship between the arterial wall and the corresponding arterial pressure, PSR is attractive because it is an indicator that is particularly relevant to a single cardiac cycle.

Newer practical techniques to estimate stiffening-related parameters, such CAVI, may have a place or it may be that other new indicators that may be more pressure independent (PSR, AASI, and sAASI) may be most useful. Not all of these techniques are fully validated, so refinements may be necessary. All techniques contain assumptions that can be seriously
questioned and none are necessarily applicable to all experimental questions or are valid over the entire range of BP values encountered in clinical medicine. For example, PWV is highly pressure dependent, but current convention does not consistently account for this important phenomenon. CAVI utilizes cfPWV, itself a hypothetical construct that does not correspond to the anatomy or function of any recognizable arterial segment, instead comprising mixed measurements taken from different parts of the circulation. SI is intrinsically local. PSR, AASI, and sAASI involve only BP measurements and may be more “global measures,” but may be relatively insensitive or too “lumped” to be clinically useful.

For clinicians, the central question about any arterial stiffness/stiffening indicator is: “Does knowing it add value?” or “What would I do differently or better in my patients if I knew these parameters?” It appears that the general answer to both questions is “not too much” for existing techniques and “too early to tell” for newer ones. Currently, the standard argument from supporters of universal PWV measurement is that it provides incremental cardiovascular disease risk stratification beyond age, BP, and other readily available risk factors. This may be true in a statistical sense but it is extremely difficult to see how such knowledge translates into better patient care. High BP is closely related to stiff arteries and there is an ongoing European trial that investigates this point further (SPATE). However, all drugs that lower arterial pressure also lower arterial stiffness. There is also the very real likelihood that stringent BP control is the only current answer. The message that there is no specific treatment for stiff arteries and the costs of professional education and quality monitoring are almost certainly overstated. In more recent studies, chronic renin–angiotensin blockade (olmesartan) has been said to lower arterial stiffness “partly independent” of the corresponding BP reduction, and there is an ongoing European trial that investigates this point further (SPATE). However, all drugs that lower arterial pressure also lower arterial stiffness. This is also the very real likelihood of misunderstanding and misrepresentation of arterial stiffness by clinicians with insufficient background knowledge or expertise. If arterial stiffness information is presented routinely to patients, the clinician must take care to convey the message that there is no specific treatment for stiff arteries and that stringent BP control is the only current answer.

Finally, although relatively inexpensive, a cost–benefit analysis is needed for arterial stiffness/stiffening indicators that should include such hidden expenses as the impact of diagnostic inaccuracies (including false positives and negatives) and the costs of professional education and quality monitoring programs. Much better understanding of the clinical and pathophysiologic information provided by stiffness and stiffening indicators is needed before their universal use by enlightened and responsible practitioners is fully warranted.

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