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## The Role of Arterial Stiffness in the Pathogenesis of Hypertension and Cardiovascular Disease

By GARY F. MITCHELL, MD

Aortic stiffening is a common but highly variable disorder that is associated with advancing age and exacerbated by many known cardiovascular disease (CVD) risk factors, including genetic factors. Increased aortic stiffness and the mismatch between aortic diameter and flow contribute to the widening of pulse pressure (PP) and development of systolic hypertension. Excessive arterial pressure pulsatility is associated with various common diseases of aging, such as CVD,<sup>1,2</sup> stroke,<sup>3,4</sup> cognitive disorders,<sup>5</sup> brain white matter lesions,<sup>6</sup> macular degeneration,<sup>7</sup> renal dysfunction,<sup>8,9</sup> and glucose intolerance.<sup>10</sup> Microvascular dysfunction is a common element in the pathophysiology of these diverse conditions.<sup>7,8,11-14</sup> Excessive pressure pulsatility, even at normotensive blood pressure levels, has adverse effects on microvascular function, suggesting that microvascular damage may represent one mechanism linking increased arterial stiffness to the foregoing age-related disorders.<sup>15</sup> High-flow organs (eg, the heart, brain, and kidneys) are particularly susceptible to these detrimental effects because pressure pulsatility penetrates further into the microcirculation when resistance to flow is low. This issue of *Cardiology Rounds* presents an overview of pulsatile hemodynamics, a summary of the techniques used to assess arterial stiffness, and relates abnormalities in aortic stiffness to the pathogenesis of hypertension and various diseases of aging.

### Pulsatile hemodynamics and measures of arterial stiffness

When the heart contracts, the resulting pulsatile flow wave generates a forward pressure wave that travels down the compliant aorta at a low pulse wave velocity (PWV) of about 4-6 m/s. The amplitude of this forward traveling wave is determined by ejection rate and local or "characteristic" impedance ( $Z_c$ ) to pulsatile flow.  $Z_c$  is the pulsatile analog of resistance and is simply the ratio of the pressure pulse ( $dP$ ) produced by a given flow pulse ( $dQ$ ) in the absence of reflected waves:  $Z_c = dP/dQ$ . Thus, increased  $Z_c$  results in a larger forward pressure wave for any given flow wave.

When the forward traveling pressure wave encounters regions of impedance mismatch, such as branch points, a partial reflection occurs. The reflection coefficient at such a junction is proportional to the degree of impedance mismatch. Innumerable such reflections summate to form a remarkably discrete global reflected wave that appears to have arisen from a single "effective" reflecting site, approximately 40-50 cm away from the heart. Reflected wave arrival time (RWAT) in the central aorta is dependent on the distance to this effective reflecting site and the spatially-averaged PWV along this path. If PWV increases and reflecting sites remain unchanged, the reflected wave will return to the central aorta earlier and augment central systolic and PP. This augmented pressure (AP) is often expressed as a fraction of central PP (CPP) to give the augmentation index,  $AI = AP/CPP$ . Obviously, CPP is simply the sum of forward wave amplitude plus any late augmented pressure due to the reflected wave. Thus, CPP is dependent on proximal aortic stiffness ( $Z_c$ ), peak aortic flow, aortic PWV, and the location and reflection coefficient of the dominant reflecting sites.

Both PWV and  $Z_c$  are directly related to aortic wall stiffness and thickness and inversely related to diameter. Their dependence on aortic wall stiffness and thickness is the same. Hence, a stiffer or thicker aortic wall is associated with proportional increases in PWV and forward wave amplitude. However,  $Z_c$  has a 5-fold greater dependence on diameter. Thus, a reduction in aortic diameter at a comparable wall stiffness is associated with a substantially larger increase in  $Z_c$  than PWV. In practice, diameter and stiffness are closely related and rarely change independently. However, if stiffening of the aortic wall is associated with a reduction in diameter,  $Z_c$  will increase much more than PWV. In contrast, if the wall stiffens and diameter increases, the change in  $Z_c$  will be attenuated as compared to the change in PWV. Thus,



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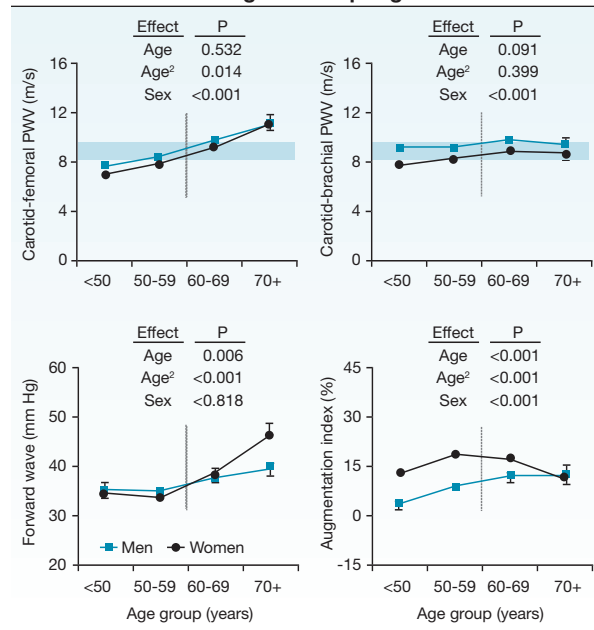
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**Figure 1: Changes in arterial properties in a health subset of the Framingham Offspring cohort.<sup>19</sup>**



patterns of relative change in Zc and PWV provide clues to the underlying biomechanics of aortic stiffening.

Based on the ostensibly straightforward assumption that reflecting sites are relatively fixed in fully-grown adults, RWAT and AI have been widely cited as easily assessed indicators of increased PWV and aortic stiffness.<sup>16</sup> However, recent studies suggest that the basic assumption of constant reflecting site location is not generally valid and that AI and RWAT are unreliable indicators of aortic stiffness.<sup>17-22</sup> To understand this paradox, it is important to note that wave reflection occurs because the waveform is traveling up an impedance gradient, from low impedance in the highly compliant aorta, to intermediate impedance in the stiffer, smaller muscular arteries, to high impedance in the resistance vessels. Data from the Framingham Heart Study have shown that with advancing age, a marked increase in aortic stiffness is accompanied by little change in muscular artery stiffness (Figure 1). As a result, by age 60 years, aortic stiffness (carotid-femoral PWV) equals, then exceeds peripheral artery stiffness (carotid-brachial PWV, shaded zone in Figure 1), reversing the normal pattern of increasing stiffness moving away from the heart. Loss of the ascending stiffness gradient reduces proximal wave reflection and shifts reflecting sites to distal regions of impedance mismatch in the smaller muscular arteries and resistance vessels. This increase in distance to the effective reflecting sites offsets the increase in PWV. As a result, RWAT changes very little across the full human lifespan despite a major increase in PWV.<sup>18,19</sup> Furthermore, AI may fall because of progressive viscous attenuation of the waveform as it travels the extra distance to the reflecting sites and back. This shift in reflecting sites distally as the aorta stiffens has 2 important implications: AI becomes more sensitive to changes in peripheral rather than central arterial properties and the protective effect of wave reflection is diminished as more pressure pulsatility is transmitted into the periphery.

In summary, disparate changes in aortic and muscular artery stiffness associated with age have complex effects on AI and RWAT that render them unsatisfactory measures of aortic

stiffness in middle-aged and older individuals. In contrast, Zc, forward wave amplitude and PWV are robust and reproducible measures of aortic stiffness in this important age range, when risk for CVD increases dramatically.

### Risk factors for increased arterial stiffness

Advancing age is a major risk factor for increased arterial stiffness. Even in populations with a low prevalence of atherosclerotic disease, carotid-femoral PWV (CFPWV) increases several-fold over the course of the average human lifespan.<sup>18,19,23</sup> However, the increase in CFPWV with age is highly variable, leading to a marked increase in population variance in the elderly. This observation suggests, and studies have shown, that additional factors modulate age-related arterial stiffening. Diabetes and obesity are leading risk factors for arterial stiffening, but many other CVD risk factors also contribute, including lipid abnormalities, sedentary lifestyle, and high salt intake.<sup>10,20,24-31</sup>

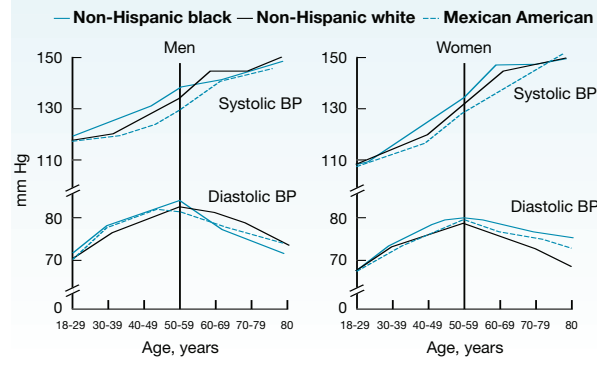
Genetic factors also contribute to the variability in arterial stiffness. Measures of arterial stiffness and wave reflection are highly heritable and family-based studies have demonstrated several regions of significant linkage using a microsatellite-based whole genome approach.<sup>32-35</sup> Genetic association studies have found relations between measures of arterial stiffness and polymorphisms in various candidate genes, including genes for the angiotensin-II type 1 receptor,<sup>36,37</sup> fibrillin-1,<sup>38</sup> angiotensin-converting enzyme,<sup>37,39</sup> alpha adducin,<sup>39</sup> aldosterone synthase,<sup>39,40</sup> endothelin A and B receptors<sup>41</sup> and matrix metalloproteinases 3 and 9.<sup>42,43</sup> However, small sample sizes and ascertainment bias (hypertensive, known coronary artery disease, etc.) may limit the generalizability of these findings. Replication of these associations in larger, community-based samples is needed in order to assess the relative contribution of variants in these and additional candidate genes to arterial stiffening in the general population. These studies will offer the opportunity to identify potential targets for development of novel pharmacologic interventions specifically aimed at preventing or reversing arterial stiffening.

### Hemodynamic correlates of increasing PP with advancing age

There is general consensus that PP provides a readily accessible measure of arterial stiffness and is an important risk factor for various diseases. However, there is debate about the mechanisms that contribute to increased pressure pulsatility. A prevailing view suggests that premature wave reflection is the primary culprit.<sup>44-46</sup> This “premature reflected wave” hypothesis portrays the aorta as a relatively inert elastic tube that breaks down as a result of lifelong pulsatile strain, leading to a dilated aorta with a stiff wall and elevated PWV. The increase in PWV is postulated to cause premature return of the reflected wave during systole, giving rise to an increase in PP.

There are problems with this seemingly straightforward reflected wave hypothesis. As emphasized repeatedly by a leading proponent of the hypothesis, the global reflected wave rarely determines peak pressure in the brachial artery, even in the elderly.<sup>47</sup> Thus, changes in reflected wave timing and amplitude are unlikely to explain the dramatic increase in peripheral PP with advancing age (Figure 2). Importantly, peripheral PP has been used in countless studies that have firmly established the link with adverse clinical outcomes. Based on this simple observation, it also seems unlikely that increased reflected wave amplitude contributes significantly to the association between

**Figure 2: Changes in blood pressure (BP) with age in various segments of the US population. Note the marked increase in pulse pressure (separation between the systolic BP and diastolic BP lines) beyond 60 years of age.<sup>48</sup>**



PP and clinical events. Furthermore, increases in AI primarily occur prior to age 60, when PP changes relatively little (Figures 1-2). AI plateaus (men) or falls (women) in patients aged >60 years, when PP increases dramatically (Figures 1-2). Thus, increased wave reflection is an unlikely explanation for most of the age-related increase in PP in individuals aged >60 years.<sup>48</sup>

The aortic wall does stiffen markedly with advancing age, as evidenced by an increase in PWV, while aortic diameter increases modestly.<sup>49,50</sup> The increase in aortic stiffness increases forward wave amplitude, which explains most of the increase in central and peripheral PP seen with advancing age. In contrast, relative wave reflection, as assessed by AI, is unchanged or even reduced in the elderly (Figure 1).<sup>19</sup> Note that the modest increase in aortic diameter offsets a component of the increase in aortic wall stiffness. As a result, in relatively healthy individuals, the increase in PWV exceeds the increases in forward wave amplitude and PP with advancing age (Figure 1).

### Hemodynamic correlates of elevated PP in systolic hypertension

The hemodynamic changes responsible for elevated PP in individuals with established systolic hypertension differ somewhat from the pattern observed with healthy aging. Patients with systolic hypertension have increased PWV and PP as compared to normotensive peers of similar age. However, PWV is sensitive to distending pressure and hypertensives generally have elevated mean arterial pressure (MAP). After adjusting for MAP, PWV no longer differs between hypertensive and normotensive groups<sup>51</sup> and may even be reduced in the muscular arteries in hypertensives.<sup>52</sup> Thus, basal differences in aortic PWV are attributable to passive differences in distending pressure. In contrast, PP and aortic Zc are much less sensitive to distending pressure and remain markedly higher in hypertensive patients after adjusting for MAP, suggesting a pressure-independent abnormality in proximal aortic function.<sup>51</sup> Since Zc and PWV have a similar relation to wall stiffness, a disproportionate change in Zc, as compared to PWV, suggests an alteration in diameter. Furthermore, the disproportionate increase in Zc indicates that the diameter must be lower in hypertensive as compared to normotensive individuals. Thus, systolic hypertension appears to be associated with a shift in the aortic pressure-diameter relation to lower values of aortic diameter at a given distending pressure, leading to higher Zc, increased forward wave amplitude, and increased PP.

The observation that aortic diameter is reduced in systolic hypertension is distinctly at odds with the established, but poorly substantiated, concept that aortic stiffening is a consequence of passive and irreversible elastin fragmentation leading to wall stiffening and lumen dilation.<sup>45</sup> However, two population-based studies provide support for the concept that increased PP is associated with reduced aortic diameter. Investigators at the Framingham Heart Study have shown that aortic diameter increases with advancing age but, at any given age, higher PP is associated with reduced aortic root diameter.<sup>49</sup> Similarly, using transesophageal echocardiography, a group from the Mayo Clinic has shown an inverse relation between PP and aortic diameter.<sup>50</sup> These findings are inconsistent with the former view of elastin fragmentation and aortic dilation.

Potential mechanisms responsible for a relative reduction in aortic diameter in the setting of systolic hypertension remain speculative. It is increasingly clear that the aorta is a dynamic organ capable of remodeling in response to physiologic stimuli. Various pathways have been identified that contribute to changes in aortic diameter following stresses such as increased flow.<sup>53,54</sup> Variability in these or other pathways could provide a mechanism whereby an increase in flow that is not accompanied by a proportional increase in diameter could lead to elevated PP. For example, obesity and diabetes are high-flow states that are associated with increased aortic diameter; however, this increase is apparently inadequate to compensate for the increase in cardiac output and peak aortic flow in these individuals because PP is generally elevated. Thus, obesity and diabetes precipitate an apparent imbalance in the relation between aortic flow and diameter that contributes to the pathogenesis of hypertension. Studies aimed at establishing the determinants of abnormal aortic diameter-flow relations offer an opportunity to define and potentially intervene in a major risk factor for elevated PP and systolic hypertension.

### Crosstalk between large artery stiffness and microvascular function

Traditionally, microvascular remodeling has been viewed in the context of autoregulation of blood flow in the setting of alterations in MAP. If mean perfusion pressure is increased and resistance in a vascular bed remains unchanged, a passive increase in flow will ensue. Autoregulatory changes in microvascular tone and structure subsequently increase vascular resistance and restore flow to nominal levels despite persistent elevation of MAP. However, studies in animal models and humans have shown that PP may also affect microvascular structure and function.<sup>55-58</sup> To test this hypothesis, we evaluated the relations between aortic stiffness and forearm microvascular function in the Framingham Offspring cohort.<sup>15</sup> Increased amplitude of the forward pressure wave and higher CFPWV were associated with a modest increase in basal resistance to mean blood flow. Additionally, the vasodilatory response to 5 minutes of forearm ischemia was markedly blunted with increasing aortic stiffness. Hyperemic forearm vascular resistance increased progressively with arterial stiffness and was approximately 2-fold higher in individuals in the highest as compared to the lowest tertiles of CFPWV and forward wave amplitude. These data from an unbiased, community-based sample suggest a steep and continuous relation between arterial stiffness and microvascular function, rather than an isolated abnormality restricted to those with established hypertension or advanced vascular disease.

Adverse effects of aortic stiffening on microvascular function may contribute to the pathogenesis of hypertension and related diseases. For example, increased cardiac output and excessive pressure pulsatility associated with diabetes or obesity may impair microvascular function, leading to elevated MAP and systolic hypertension. Furthermore, in settings where PP and MAP change discordantly, dual responsiveness of the microcirculation to MAP and PP may adversely affect basal and hyperemic blood flow in central organs. Advanced age is associated with a marked increase in PP with no change or a modest fall in MAP.<sup>59</sup> If local vascular resistance in an organ increases in response to excessive PP, yet MAP remains unchanged or falls, then blood flow to that vascular bed will necessarily fall, resulting in relative ischemia at rest. Furthermore, structural remodeling in the microcirculation may limit reactivity in response to fluctuations in metabolic demand or blood pressure, ultimately leading to end-organ dysfunction or damage.

Adverse effects of arterial stiffening on the microcirculation are amplified in settings that increase forward transmission of pressure pulsatility. Aortic stiffening increases pulsatility and the associated loss of the stiffness gradient between aorta and muscular arteries reduces wave reflections and, therefore, favors transmission of more of that pulsatility into the microcirculation. Similarly, high basal blood flow (low impedance) limits the damping that normally occurs in the resistance vessels and, therefore, favors transmission of pulsatility into the capillaries. High-flow organs such as the heart, brain, retina, and kidney are all particularly susceptible to excessive pressure pulsatility for this reason. This susceptibility is enhanced by conditions that further increase resting flow, such as smoking, diabetes, and lipid abnormalities,<sup>15</sup> potentially explaining a component of the known relation between these risk factors and various microvascular disorders, including microvascular angina, vascular cognitive impairment, senile macular degeneration, and chronic renal failure. More work is needed to further define the implications of these relations and determine whether interventions aimed at preventing or reversing arterial stiffening will prevent the considerable morbidity associated with damage in these vascular beds.

### **Abnormal large artery stiffness is a modifiable risk factor**

As emphasized throughout this report, the past decade has witnessed a transition in our understanding of the role of arterial properties in the pathogenesis of disease. In the past, aortic properties were often ignored or the aorta was portrayed as a passive conduit with woven elastic walls that eventually, and more or less inevitably, broke down in the face of a lifetime of pulsatile strain. Recent studies have demonstrated that aortic stiffness is modifiable, often within a relatively short period of time. Several lifestyle interventions have been shown to reduce arterial stiffness.<sup>60</sup> Aerobic exercise has a favorable effect on large artery stiffness,<sup>26,27,61</sup> whereas weightlifting may have an adverse effect.<sup>62</sup> Obesity is an important risk factor for increased arterial stiffness<sup>28</sup> and weight loss appears to reduce stiffness.<sup>63</sup> A low salt diet also appears to have a favorable effect on central arterial properties.<sup>24,64</sup> The Dietary

Approaches to Stop Hypertension (DASH) diet has been shown to reduce PP, suggesting a favorable effect on large artery function.<sup>65</sup>

Among possible pharmacologic interventions, those that block the renin-angiotensin-aldosterone system appear to be particularly effective at reducing arterial stiffness. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are both effective at reducing measures of aortic stiffness, including Zc and CFPWV.<sup>66-69</sup> Low-dose diuretics reduce PP and aortic stiffness.<sup>70,71</sup> Furthermore, sodium restriction or the addition of a low-dose diuretic enhances the favorable arterial effects of ACE inhibition or an ARB.<sup>72</sup> Aldosterone also appears to contribute to arterial fibrosis and stiffening and aldosterone antagonists may reduce arterial stiffness, although clinical data remain limited and inconsistent.<sup>73-76</sup>

Dihydropyridine calcium channel blockers (CCBs) have limited direct effects on aortic stiffness. Nifedipine is less effective than lisinopril at reducing pulse wave velocity and this difference is associated with blunted regression of left ventricular hypertrophy.<sup>77</sup> The recently completed Conduit Artery Function Evaluation (CAFE) Study compared the on-treatment hemodynamics of amlodipine-based therapy (with add-on ACE inhibition) versus atenolol-based therapy (with add-on diuretic) and found no difference in CFPWV, suggesting that aortic stiffness was unaltered.<sup>78</sup> Furthermore, amplitude of the forward pressure wave, estimated from the early peak of a central pressure waveform, was actually higher in the CCB group, indicating either increased flow or a stiffer proximal aorta with CCB, which has been reported previously.<sup>79</sup> In CAFE, central PP was lower with CCB-based therapy because of a reduction in AI; however, as noted by the authors, this reduction was attributable to a higher heart rate in the amlodipine group. Higher heart rate (shorter systolic ejection period) is associated with less overlap between the forward and reflected waves, leading to less late systolic central pressure augmentation even if reflected wave timing and amplitude remain unaltered. Thus, CCBs do reduce AI and central PP; however, the reduction in AI is not indicative of any change in aortic stiffness.<sup>17</sup>

An important unanswered question is whether tailoring antihypertensive therapy to hemodynamic abnormalities improves hypertension control and enhances the clinical benefits of treatment. Arterial properties can now be assessed reproducibly using noninvasive techniques, and antihypertensive medications have been shown to have differing effects on the mean and pulsatile components of hemodynamic load. Therefore, it is possible to target specific therapy to the hemodynamic profile of a given patient. Thus, a patient with a primary abnormality in MAP might be preferentially treated with a resistance vessel dilator, such as a CCB, whereas a patient with an isolated increase in PP might instead be treated with a low-dose diuretic and an ACE inhibitor or ARB as first-line therapy. A more complex combination of medications may be required in patients with mixed hemodynamic abnormalities. For example, a combination of elevated MAP, PP, and cardiac output might be found in overweight or obese patients with longstanding hypertension. Obviously, exercise and weight loss would be key interventions in such cases; however, in addition, a more complex combination of a low-dose

diuretic and an ACE inhibitor or ARB (for the large vessels) plus a CCB (to further reduce vascular resistance) may be required to control blood pressure. Unfortunately, this concept has not yet been evaluated in a systematic fashion and, thus, potential benefits of targeted therapy remain speculative.

## Conclusions

Abnormal arterial stiffness is highly prevalent in the elderly, exacerbated by common CVD risk factors and closely related to various adverse clinical outcomes, both in cross-sectional and prospective evaluations. A number of lifestyle and pharmacologic interventions are effective at reducing arterial stiffness and, therefore, offer an opportunity to reduce the apparently considerable burden of disease attributable to excessive pressure pulsatility. Well-planned clinical trials are needed to confirm these associations and establish the effects of therapy targeted at reducing arterial stiffness.

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**Disclosure:** Dr. Mitchell is owner of Cardiovascular Engineering, Inc., a company that designs and manufactures devices that measure vascular stiffness, and is a member of the advisory board of OMRON Healthcare.

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