Aortic Diameter, Aortic Stiffness, and Wave Reflection Increase With Age and Isolated Systolic Hypertension

Michael F. O’Rourke, Wilmer W. Nichols

The October 2004 High Blood Pressure Research Council meeting of the American Heart Association included a debate on the proposition that “aortic diameter, aortic stiffness, and wave reflection all increase with age and in isolated systolic hypertension.” This was stimulated by a series of articles1–5 that took a contrary position to change in aortic systolic hypertension. This was stimulated by a series of

Observations and Measurements

“Premature arterial senility” as a cardiovascular risk factor has long been of intense interest in actuarial studies, even before introduction of the cuff sphygmomanometer,6 as it had been in clinical medicine. The latter is apparent in the textbooks of Osler and Mackenzie >100 years ago.7,8 In these, premature arteriosclerotic change was assessed from the pulse waveform palpated at the wrist or measured from the radial artery by sphygmography. The first graphic recording studies of the arterial pulse by Marey in 18639 noted characteristic differences between young and old persons (Figure 1), with prominent late systolic augmentation (“tidal wave”) in the latter. Mahomed10,11 confirmed these changes in the 1870s, stressing that “the tidal wave is prolonged and too much sustained,” and noting similar pulse waveform changes in asymptomatic persons with elevated arterial pressure as well as in the elderly. By 1900, these findings were used by life insurance companies to decline applicants on the basis of premature arterial senility.6

The cuff sphygmomanometer was introduced in the early 1900s, and by 1916, data had been presented to show the relationship between risk of death and systolic pressure in asymptomatic persons.6 For decades thereafter, aging change in arteries was gauged by change in arterial pressure, especially systolic and pulse pressure.15,16 But brachial systolic pressure increases by only ≈25 mm Hg on average (≈22%) between ages 20 and 80 years. Recent studies on central and aortic pressure allow for the normally high amplification of upper limb systolic pressure in youth and show that central (aortic) systolic and pulse pressure increase by 35 to 40 mm Hg between 20 and 80 years of age (ie, systolic by ≈40% and pulse pressure by >100%12,17 (Figure 2). Such change is generally attributed to arterial stiffening with age and return of reflected waves from the periphery to the heart.12 When stiffening is measured as “aortic” pulse wave velocity, there is an ≈100% increase between ages 20 and 80 years18 (Figure 3). However, in contrast, there is little increase with age in pulse wave velocity within muscular conduit arteries of the limbs,5,18,19 There is also little difference between males and females,5,18,19

Increase in aortic diameter with age is usually invoked to explain progressively increasing prominence of the aortic knuckle in routine chest radiographs. Autopsy studies have shown a clear-cut increase in aortic surface area with age20 (Figure 4), whereas cross-sectional studies of aortic diameter by angiography21 and ultrasound22–26 have shown lesser, but still definite, increase with age, except in the most proximal part of the ascending aorta. Gender differences are largely explicable on the basis of smaller body size in women.12,19 There is some controversy on the competing effects of age, and of blood pressure change accompanying age, on aortic dilation. Cross-sectional studies cannot be expected to resolve this issue. A comparison between hypertensive and matched normotensive subjects showed a greater degree of aortic dilation in the latter.20 Longitudinal studies in patients with Marfan syndrome and cystic aortic necrosis have shown progressive aortic dilation with age but with rate of dilation decreased by antihypertensive therapy.27 Cross-sectional studies have shown aortic dilation in cystic aortic necrosis with Marfan syndrome related to central but not brachial pulse pressure.28

Pathological studies of the aging human aorta29,30 have shown that thickness of the load bearing media remains relatively constant throughout life and that wall thickening is attributable predominantly to increased width of the intimal layer. There is thinning, fraying, and fracture of the elastin fibers, together with collagenous remodeling (Table), and
progressive disorganization of the media with, ultimate development of cystic medial necrosis. Such medial necrosis in the elderly is described in pathology textbooks as similar to that seen in an early age in Marfan syndrome and to be the substrate of aortic dissection, dilation, and rupture.

**Interpretations and Explanations**

Conventional explanations of all aortic changes with age are based on the physical principles of fatigue and fracture because these affect the inert elastin fibers within the aortic media. Elastin is the most inert substance in the body, with a chemical half life measurable in decades. The same principles of a material fatigue, as applied to natural rubber, predict fracture after some 10⁹ cycles of 8% stretch, which is achieved in the proximal aorta within 40 years of life. Fracture is not expected within this time span, when stretch is <5%, which explains relative immunity of the peripheral muscular arteries from this process.

Fracture of the elastin fibers readily explains dilation and stiffening of the aorta with age. Elastin fibers normally bear aortic stresses. When they give way, the wall stretches and the vessel dilates; stresses are then transferred to the less extensible collagenous elements in the wall, just as stresses are so transferred when pressure rises in the normal artery. The latter phenomenon explains the well-known nonlinear pressure/diameter relationship in arteries.

Increased stiffness of the aortic wall causes corresponding increase in aortic pulse wave velocity. Such increase in wave velocity causes the reflected wave from the peripheral arteries to return earlier to the heart and to boost (augment) pressure in late systole rather than in early diastole. Such increase in wave velocity, with movement of the reflected wave from diastole into systole, explains the change in pulse waveform with age, as described by Marey, Mackenzie, Mahomed et al, and referred to above. Mahomed pointed out in 1872 that late systolic augmentation of the pulse was always greater in the brachial than radial artery and greater still in the carotid artery. This was confirmed by Kelly et al, who also showed in normal subjects that from 30 years onward, the late systolic peak dominates over the early systolic peak in the carotid and other central arteries whereas the early peak or shoulder corresponds with peak.
systolic flow. In older subjects, this shoulder on the upstroke of the pressure wave is followed by a surge of pressure in late systole caused by early return of wave reflection (Figure 5). In the elderly, the reflected wave arrives even earlier in systole and merges (or blends) with the incident (or forward) pressure wave so that there is no inflection point.12,21 These clinical studies confirmed earlier studies in experimental animals and in computer models of the systemic arterial tree.37–40 These expressed pulsatile pressure/flow relationships as vascular impedance and showed that the ill effects of aortic stiffening could be explained on the basis of increase in stiffness of the proximal aorta (increased characteristic impedance) and early wave reflection, which shifted impedance curves to higher frequencies12,37–41 (Figure 5). The combined effect was to increase markedly the impedance to left ventricular ejection over the frequency band (1 to 4 Hz), which normally contains the greatest energy of the left ventricular ejection (flow) wave.

Figure 2. Change in brachial systolic pressure with age in multiple population studies70–74 shows a steep rise from age 5 years to plateau when full body height is reached at age 18, then a subsequent rise after age 45. Aortic systolic pressure, measured at cardiac catheterization,19 increases progressively with age. After Nichols and O’Rourke.12

Figure 3. Changes in aortic pulse wave velocity (PWV; between the aortic root and the femoral artery at the groin) with age in a group of 480 human subjects with low prevalence of atherosclerosis in urban Beijing. From Avolio et al.18

Figure 4. Increase in surface area of the thoracic aorta with age in men (left) and in women (right), from the unselected autopsy study of Mitchell and Schwartz.20
Implications

Effects of wave reflection are readily measured in terms of augmentation of the central (carotid, aortic, and left ventricular) pressure waveform. The aortic and left ventricular waveforms may be measured invasively during cardiac catheterization41–43 or synthesized from the radial pressure waveform recorded by applanation tonometry using a Food and Drug Administration–approved process.12,44 The carotid waveform may be recorded directly by applanation tonometry1–5,34–36,44,45 or approximated from the carotid diameter waveform.46 Measurement of augmentation requires identification of the localized peak, systolic shoulder, or inflection, which corresponds to peak aortic flow34,41 (Figure 5). This requires accurate dynamic frequency response of sensor, recorder, and convolutional process and has not been achieved in some clinical studies, as discussed specifically by Chen et al47 and Smulyan et al.43

The principal implications of aortic change with age relate to their magnitude, their effects on left ventricular function, and opportunities for therapeutic modification. It is clear (Figure 2) that conventional measurements of brachial systolic and pulse pressure underestimate the aging effect, and that aortic systolic and especially aortic pulse pressure increase far more with age than is usually perceived.12,16,17 Such changes are largely responsible for development of left ventricular hypertrophy and left ventricular dysfunction with age48 as well as renal dysfunction49,50 and progression of atherosclerosis.51 Changes can be best quantified from measurements of vascular impedance or inferred from augmentation of the central arterial pressure pulse. Augmentation of the pulse depends on the pattern of left ventricular ejection as well as on wave reflection and is decreased when left ventricular systolic function is impaired.52 Inability to maintain late systolic ejection with age12,21 may be responsible for the relative flattening of carotid34 and of calculated aortic augmentation53 with age.

Knowledge of arterial change with age permits a more logical approach to drug therapy of the diseases associated with age, such as isolated systolic hypertension, cardiac failure, and angina pectoris. From what has been described

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Young</th>
<th>Old</th>
<th>Change %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D (mm)</td>
<td>17.0</td>
<td>22.4</td>
<td>31.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WT (mm)</td>
<td>0.94</td>
<td>1.40</td>
<td>49.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ILS (µm)</td>
<td>8.7</td>
<td>12.0</td>
<td>37.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EFD (LU/mm)</td>
<td>125</td>
<td>36</td>
<td>-71.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MT (µm)</td>
<td>0.79</td>
<td>1.00</td>
<td>26.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T/LU (dyne/cm²)</td>
<td>1236</td>
<td>1891</td>
<td>53.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

D indicates, pressure-fixed external diameter; WT, wall thickness; ILS, interlaminar spacing; EFD, elastin fiber density (lamellar units/mm); MT, medial thickness; T/LU, calculated (at mean pressure 100 mm Hg) tension per lamellar unit.

*From O’Rourke et al.30

Age-Related Changes of Elastin Lamellae in the Human Mid-Thoracic Aorta for Young (18–40 years) and Old (56–58 years) Persons who Died From Noncardiovascular Disease

![Figure 5. Effects of aging on aortic pressure wave contour (time domain) and aortic impedance modulus (frequency domain). Top shows aortic pressure waves (above) and flow waves (below) in a young (left) and old (right) adult. Bottom shows impedance modulus (vertical axis) plotted against frequency in a young (at left) and old subject (at right). Increased proximal aortic stiffness with age causes increased amplitude of the initial pressure peak and increase in characteristic impedance (arrow 1). Earlier return of reflected waves from arterial terminations causes the pressure peak to move into late systole and the impedance curve to shift to the right (arrow 2). The peak of flow corresponds to the early systolic pressure peak in the young subject and to the inflection on the rising limb of pressure in the older subject. After O’Rourke.39](http://hyper.ahajournals.org/)

from pathological aortic change, it is difficult to envisage that drugs would have any major direct effect on the disorganized aged aorta. Such beneficial effects have been sought and described for the vasopeptidase inhibitor omapatrilat2 and for the age cross-link breaker AT711,54 but effects have not been substantial. No direct effect on aortic stiffness has been found for nitrates in older human adults.55–57 In very carefully controlled experimental studies on animals, nitrates have shown no direct effect on aortic characteristic impedance, despite marked effect on peripheral muscular arteries.58

In contrast to inefficacy on aortic stiffness, nitrates and other arterial dilators have marked effects on wave reflection and can virtually eliminate the late systolic augmentation.
caused by early wave reflection.56,59 Because this effect is confined to wave reflection, it may not be apparent when pressure is measured in the upper limb.60,61 Beneficial effect of nitrates on wave reflection14,56 can be explained on the basis of arterial dilation and of “trapping” of reflected waves in the peripheral vessels so that they do not return to the heart. Such reduction in wave reflection is achievable in low dosage without any effect on arterioles or on peripheral resistance.56,59 Most data on wave reflection have come from use of nitrates because the effect is immediate and dramatic. However, similar effects been described for perindopril and other drugs used for treatment of hypertension.13,62

**Reservations on a Contrary View**

There is no argument that the aorta and proximal arteries stiffen with age, whereas peripheral muscular arteries are less affected.5,18,19 There is no argument that the more distal segments of the proximal thoracic aorta dilate with age, but there is debate over whether this change is induced by age or by arterial pressure. Mitchell et al3,63 argue that “effective aortic diameter” measured indirectly using the water hammer equation is reduced in persons with isolated systolic hypertension. Such a view gains some support from Framingham data,24 which showed, after correction for age, that there is an inverse relationship between aortic diameter and brachial pulse pressure; similar findings were reported by Agmon et al from Mayo.25 In both of these studies, any pressure effect was trivial after correction for age, body size, and gender. Such a pressure-related effect may have been related to therapy (more than one third of the Agmon study group were receiving antihypertensives) or to the measuring site for pressure. Jondeau et al28 found no association between aortic diameter and brachial pulse pressure but a definite relationship of diameter with aortic pulse pressure in patients with Marfan syndrome. The Framingham group24 noted that an initially narrow aorta predisposes to higher pulsatile flow and higher pulse pressure. The concept of effective aortic diameter and its derivation was challenged by us64 on multiple grounds. The water hammer formula is only valid in a reflectionless system and must have pressure and flow measured at the same site and pulse wave velocity measured locally.12,64 Mitchell et al3 measured pressure in the carotid artery, blood flow velocity in the left ventricular outflow tract, and pulse wave velocity from the central aorta to the femoral artery.

Mitchell et al3 downplayed the effect of wave reflection with age, noting in a select healthy population within the Framingham group (<20% of all) that carotid augmentation index decreased with age in women, although increasing in men, whereas amplitude of the forward wave increased in both genders with age. Such discordant gender differences for augmentation have not been reported previously, nor has decrease in augmentation with age. There were other anomalies in this article that we have questioned,64–66 including the calculation of forward pressure amplitude, reflected wave transit time, and greater distance to reflecting site (rather than reduced distance that we have described).12,21 All of these measurements depend on correct determination of the inflection point64,41 (Figure 5).

Anomalies in the Mitchell articles may be methodological and related to the detection of the initial systolic shoulder in the carotid tracing (or inflection point; Figure 5). We have experienced problems with our processing of the carotid pressure waveform and have noted far greater variability with such waveforms than when we have synthesized the aortic waveform from the radial wave.57 In the second Australian High Blood Pressure (ANBP2) study, the experienced group of Cameron et al45 noted wide variation in the time from wave foot to inflection point of 5 to 300 ms and corresponding wide variation in calculated augmentation index. Their average value of 80 ms was half the value for their invasive study of aortic pressure in which augmentation index was unusually low.68 As reported by the ANBP2 group, there was no relationship between augmentation index and cardiovascular events, whereas others69 have found a positive association. This important issue comes down to the accuracy with which one can identify the inflection point or shoulder that corresponds to the peak of flow in the artery and that may be blended with the foot of the reflected wave.12,21 If this is identified too early, augmentation will be calculated high and characteristic impedance low; if identified too late, augmentation will be low and characteristic impedance falsely high. It is not possible to exclude such problems in interpretation of the Mitchell data.

Until and unless the problems raised above can be excluded, the conventional approach, discussed here (with mutually supportive data from a variety of sources, all logically explicable) remains strong.

**References**


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