



## Aging and Arterial Stiffness

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Arterial walls stiffen with age. The most consistent and well-reported changes are luminal enlargement with wall thickening and a reduction of elastic properties at the level of large elastic arteries. Longstanding arterial pulsation in the central artery causes elastin fiber fatigue and fracture. Increased vascular calcification and endothelial dysfunction are also characteristic of arterial aging. These changes lead to increased pulse wave velocity, especially along central elastic arteries, and increases in systolic blood pressure and pulse pressure. Vascular aging is accelerated by coexisting cardiovascular risk factors, such as hypertension, metabolic syndrome and diabetes. Vascular aging is an independent risk factor for cardiovascular disease, from atherosclerosis to target organ damage, including coronary artery disease, stroke and heart failure. Various strategies, especially controlling hypertension, show benefit in preventing, delaying or attenuating vascular aging. (*Circ J* 2010; **74**: 2257–2262)

**Key Words:** Aging; Stiffness; Vasculature; Hypertension

Arterial walls stiffen with age. The most consistent and well-reported changes are luminal enlargement with wall thickening (remodeling) and a reduction of elastic properties (stiffening) at the level of large elastic arteries, namely arteriosclerosis.<sup>1</sup> Interestingly, this aging process in the arterial tree is heterogeneous, with distal muscular arteries not exhibiting these stiffening changes, which is different from the atherosclerotic process.<sup>2</sup>

The media of large arteries is mainly composed of an integrated assembly of vascular smooth muscle cells and elastic and collagen fibers, comprising functional musculoelastic sheets. Cross-links between extracellular matrix components and smooth muscle cell–matrix interactions confer adequate mechanical properties.<sup>3</sup> The principal structural change with aging is medial degeneration, which leads to progressive stiffening of the large elastic arteries. Longstanding arterial pulsation in the central artery has a direct effect on the structural matrix proteins, collagen and elastin in the arterial wall, disrupting muscular attachments and causing elastin fibers to fatigue and fracture.

Accumulation of advanced glycation endproducts (AGE) on the proteins alters their physical properties and causes stiffness of the fibers. Another major change in the arterial wall is calcium deposition. The calcium content of the arterial wall increases with age, particularly after the 5th decade, which might also contribute to the loss of arterial distensibility.<sup>4</sup>

Though the structure of the peripheral muscular arteries/arterioles is only minimally affected by aging, impaired vasomotor function associated with endothelial dysfunction leads to thickening of the intima–media layer, and can contribute to peripheral resistance.<sup>5,6</sup> Endothelial dysfunction is characteristic of arterial aging, triggered by a decrease in antioxidative capacity and an increase in oxidative stress.<sup>7,8</sup>

Moreover, Qiu et al recently suggested that, as well as changes in the extracellular matrix, increased stiffness of the vascular smooth muscle cells themselves also mediates aging-associated vascular stiffness by increasing adhesion molecule expression.<sup>9,10</sup>

Finally, various comorbid risk factors, which are invariably highly prevalent among the elderly, accelerate the atherosclerotic process. Age-related changes in the arterial structure may create a vicious cycle of arterial stiffness. Wide pulse pressure is transmitted to other arteries, such as the carotid, which further aggravates the process of large artery remodeling to reduce wall stress, leading to intima–media thickening.<sup>11</sup>

The causes of vascular aging are summarized in **Figure 1**.

### Assessing Arterial Stiffness

Several non-invasive methods are currently used to assess vascular stiffness.<sup>12</sup> Pulse wave velocity (PWV) and the augmentation index (AI) are the 2 major non-invasive methods of assessing arterial stiffness.

PWV reflects the elasticity of the segmental artery. Cardiac contraction generates a pulse wave, which is propagated distally to the extremities. PWV is calculated as the distance traveled by the pulse wave divided by the time taken to travel the distance.<sup>13</sup> Increased arterial stiffness results in increased speed of the pulse wave in the artery. PWV can be measured in any arterial segment between 2 regions. Carotid–femoral PWV is considered as the gold standard for assessing central arterial stiffness,<sup>14</sup> and is an independent predictor of cardiovascular mortality and morbidity in elderly subjects,<sup>15,16</sup> as well as in the general population.<sup>17,18</sup> However, a relatively high level of skill combined with the need to expose the

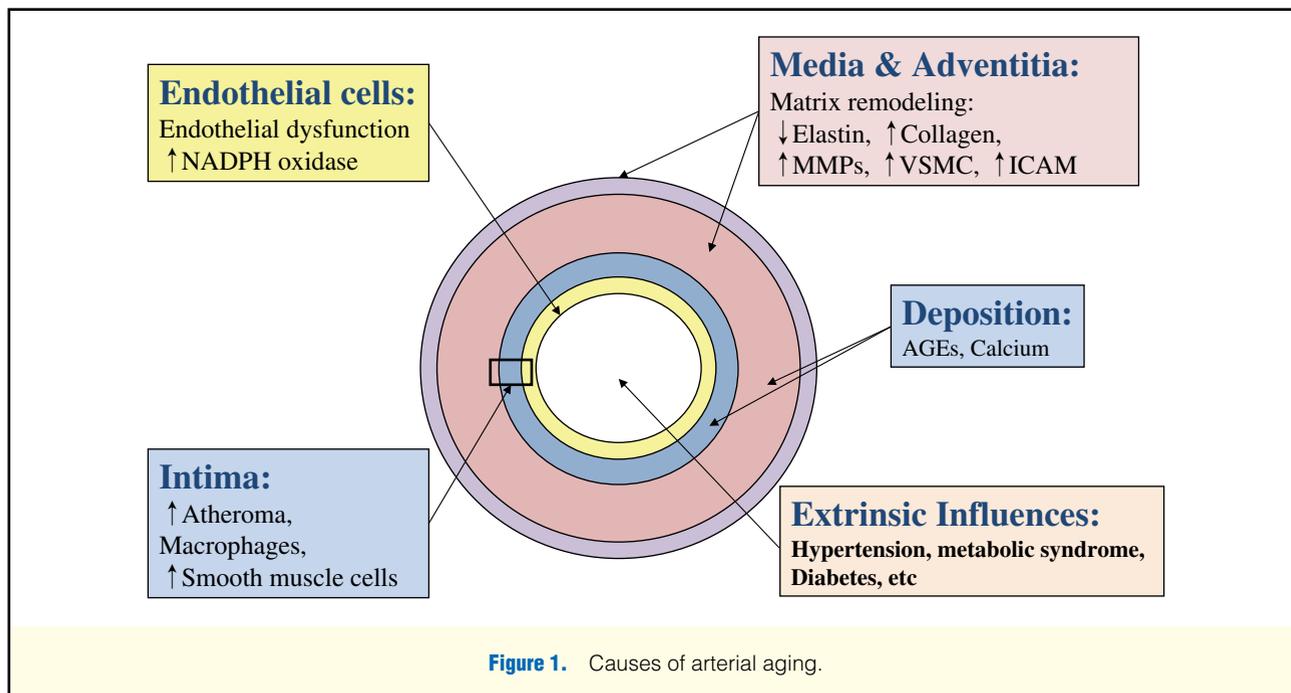
Received September 13, 2010; accepted September 14, 2010; released online October 15, 2010

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ISSN-1346-9843 doi:10.1253/circj.CJ-10-0910

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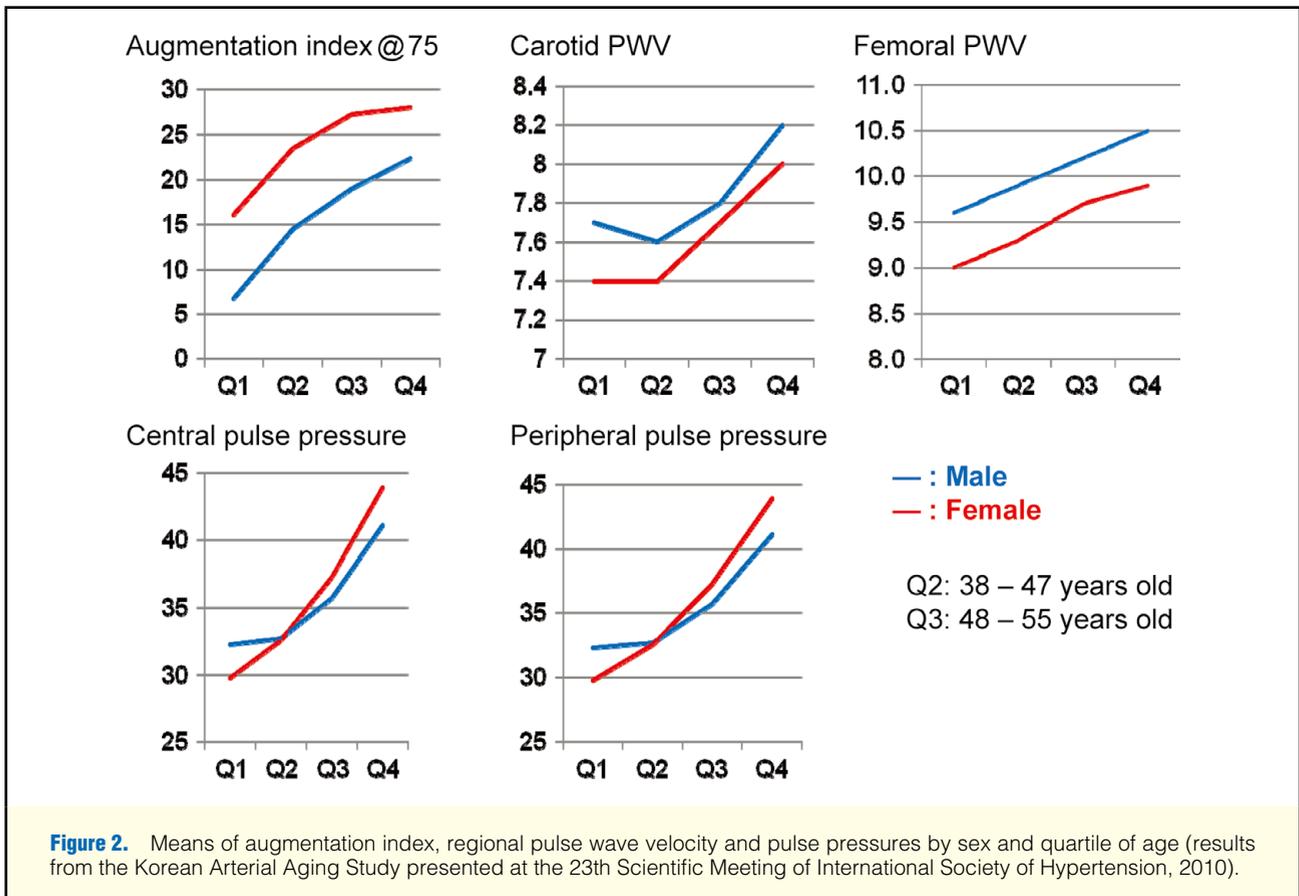
inguinal region are barriers to its wide clinical use. In contrast, the brachial–ankle PWV is easy to measure and has potential for screening purposes. In small studies, brachial–ankle PWV was an independent predictor of cardiovascular death and events in elderly community dwelling people<sup>19</sup> and in patients with coronary artery disease.<sup>20</sup> Though brachial–ankle PWV reflects not only elastic central arterial stiffness but also muscular peripheral arterial stiffness,<sup>21</sup> it shows a close correlation with aortic or carotid–femoral PWV.<sup>22</sup> The main limitation of PWV interpretation is that the PWV is significantly influenced by blood pressure (BP). Because increased BP increases the arterial wall tension, thus adding functional stiffening of the arteries, BP becomes a confounding variable when comparing the degree of structural arterial stiffening. The stiffness index,  $\beta$ , can be derived with minimal influence of BP; however,  $\beta$  is a marker of regional and not segmental arterial stiffness.<sup>13</sup> Because  $\beta$  is estimated at the same site of PWV measurement, but with an adjustment for BP, it cannot be used to obtain segmental arterial stiffness when the BP differs between the proximal and distal parts of the measured segment. Recently, a new arterial stiffness index, the cardio-ankle vascular index (CAVI), has been suggested as a marker of arterial stiffness independent of BP.<sup>23</sup> CAVI is derived by measuring PWV and then adjusted by the stiffness parameter,  $\beta$ , thus enabling BP-independent measurement of arterial stiffness. Indeed, early results show good reproducibility, BP-independence, and risk predictability;<sup>24</sup> however, further studies are warranted for wide acceptance.

AI reflects stiffness of the systemic arterial tree.<sup>25</sup> The arterial pressure wave is a composition of the forward pressure wave arising from left ventricular ejection and the backward (reflected) pressure wave. Backward pressure occurs mainly as a consequence of wave reflection and wave reflection is mainly created by impedance mismatch at the branch point of the arterial system and very small resistance arterioles. The interaction between the forward and reflected pulse waves is assessed by pulse wave analysis and expressed as the AI. The pressure waveform from the radial artery is recorded

non-invasively with applanation tonometry, and then the aortic pressure waveform is derived by a generalized transfer function (Sphygmocor, AtCor, Sydney, NSW, Australia).<sup>26</sup> Therefore, central arterial stiffness and peripheral reflectance are important determinants of the AI. Normally, the reflected wave arrives at the aortic root during diastole and augments the coronary circulation. Increased stiffness of the aorta increases the aortic PWV and the reflected wave returns earlier to the aortic root during late systole when the ventricle is still ejecting blood, adding the reflected wave to the forward wave and augmenting the central systolic pressure. Increased central systolic pressure and pulse pressure result in an increase in arterial wall stress, progression of atherosclerosis and the development of left ventricular hypertrophy because of increased left ventricular afterload.<sup>27,28</sup> Early return of the reflected wave also causes a decrease in central diastolic pressure,<sup>29</sup> AI is also influenced by BP<sup>30</sup> and, importantly, by heart rate.<sup>31</sup> Though brachial systolic BP is not influenced by heart rate, central BP is significantly increased by heart rate reduction, which can be a confounding factor.

### Age-Sex Effects on Arterial Stiffness

A number of studies have investigated the effects of age on aortic PWV and AI.<sup>2,32,33</sup> Most studies suggest a linear, age-related increase in both PWV and AI; however, central AI and aortic PWV do not always show a linear correlation, but rather they are differentially affected by aging.<sup>32</sup> Data from a large cohort of healthy individuals in the Anglo-Cardiff Collaborative Trial (ACCT) showed these different patterns in age-related changes between central AI and aortic PWV. Changes in AI were more prominent in younger individuals (<50 years), whereas the changes in aortic PWV were more marked in those older than 50 years. Therefore, central AI might be a more sensitive marker of arterial aging in younger individuals, and aortic PWV is more sensitive in those over 50 years of age. Similarly, Mitchell et al reported that central



AI changes less with age in older individuals and actually declines after the age of 60 years.<sup>2</sup> McEniery et al suggested a hypothesis for those discrepant responses.<sup>32</sup> In younger individuals, the rise in augmented pressure is because of an increase in the magnitude of wave reflection rather than increased wave velocity, whereas in older individuals, the rise in augmented pressure is driven by an earlier return of the reflected wave and a less compliant aorta rather than predominant changes in the magnitude of wave reflection. Age-related dilatation usually occurs in large arteriosclerotic arteries,<sup>34</sup> thus increasing PWV, but minimally affecting impedance.<sup>35,36</sup>

Though it is still controversial, there is a reported greater increase in aortic stiffness with age among women, particularly with the menopause. In particular, AI is higher in women than in men by approximately 7% after menopause, in part because of women's shorter height and therefore closer physical proximity between the heart and reflecting sites.<sup>2,37</sup> Another report found a steeper age-related rise in pulse pressure among women after menopause.<sup>38</sup> Central PWV also increases more rapidly with age in women than in men, crossing over around the age of 45 years, whereas there is no significant difference across the sexes in femoral PWV.<sup>39</sup>

Recently, a Korean vascular research working group performed the Korean Arterial Aging Study (KAAS) to determine the effect of aging on the stiffness parameters such as AI and PWV in apparently healthy individuals with or without CV risk factors.<sup>40</sup> That study enrolled 1,750 subjects aged 17–87 years (mean, 46.5 years) who were apparently healthy and not taking any medication for hypertension, diabetes or dyslipidemia. We observed the same tendency in the aging and sex effects. In younger ages (age quartile 1 and 2), both

central and peripheral pulse pressures were lower in women than in men, but around 45 years, the pulse pressures of the women sharply rose, so that in their 50s and over, women had higher pulse pressures than men. The same tendency of a rapid increase was observed in central pulse wave velocity (Figure 2).

### Clinical Significance of Aging-Associated Arterial Stiffness

Once, the aging-associated changes in arterial structural and functional changes were thought to be part of normative agings, but this concept changed when data emerged showing that these changes are accelerated with coexistent cardiovascular disease. For example, patients with hypertension,<sup>41</sup> metabolic syndrome,<sup>42</sup> or diabetes<sup>43</sup> exhibit increased carotid wall thickness and stiffness even after adjusting for age. And this 'accelerated' arterial aging is well confirmed to be a risk.

Stiffening of large arteries results in various adverse hemodynamic consequences. Aging-associated arterial stiffness leads to a rise in pulse pressure and isolated systolic hypertension. Following aging, systolic BP increases linearly, while diastolic BP increases until approximately age 50 then declines.<sup>44</sup> Mean arterial pressure increases until approximately age 50 then reaches a plateau, while pulse pressure is constant until approximately age 50 and then increases. In individuals over 60 years of age, isolated systolic hypertension affects more than 50%, and results in excess morbidity and mortality. Increased pulsatile pressure and flow stresses extend to the vulnerable microcirculation of vasodilated organs, such as the brain and kidneys, and can predispose to

cerebral lacunar infarction and albuminuria. Indeed, isolated systolic hypertension caused by widening of pulse pressure is the most common form of hypertension among the elderly,<sup>33</sup> and carries a 3-fold increase in the risk of stroke. Moreover, arterial stiffness correlates with cognitive function in the very elderly over 80s.<sup>45</sup> Elevated systolic BP because of large arterial stiffening also promotes left ventricular hypertrophy and ventricular stiffening, thus leading to diastolic dysfunction and heart failure, the incidence of which doubles among isolated systolic hypertensive patients.<sup>46,47</sup> In addition, low diastolic pressure reduces coronary blood flow, aggravating the situation and predisposing to ischemia.

### Management of Arterial Aging

There are a large number of studies reporting changes in arterial stiffness and wave reflection after various interventions, either non-pharmacological or pharmacological.<sup>13</sup> Non-pharmacological treatments that are able to reduce arterial stiffness include exercise training, weight loss, and various dietary modifications, including low-salt diet, moderate alcohol consumption, garlic powder,  $\alpha$ -linoleic acid, dark chocolate, and fish oil.<sup>48</sup> Pharmacological treatments include (1) antihypertensive treatment such as diuretics,  $\alpha$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), and calcium-channel antagonists;<sup>49</sup> (2) treatment of congestive heart failure, such as with ACE inhibitors, nitrates,<sup>50</sup> and aldosterone antagonists;<sup>51</sup> (3) lipid-lowering agents such as statins;<sup>52,53</sup> (4) antidiabetic agents, such as thiazolidinediones;<sup>54</sup> and (5) AGE breakers.<sup>55</sup>

It is still debated whether the reduction in arterial stiffness after antihypertensive treatment is only attributable to BP lowering, or if additional BP-independent effects are involved.<sup>48</sup> However, renin-angiotensin-aldosterone system (RAAS) inhibitors, such as the ACE inhibitors and ARBs, have been widely suggested to have a BP-independent effect on arterial stiffness.<sup>56-64</sup> Those observations are relevant to the widely reported fibrosis-inducing effect of the RAAS. In contrast,  $\beta$ -blockers has been suggested to be inferior to other classes of drugs in reducing vascular stiffness because  $\beta$ -blockers devoid of vasodilating properties are less effective for reducing central pulse pressure and AI than other antihypertensive drugs.<sup>13</sup> Indeed, non-vasodilating  $\beta$ -blockers may increase vasoconstriction and facilitate the return of wave reflection in late systole rather than in diastole, thereby increasing the AI. All of these factors contribute to an impedance mismatch between the heart and the arterial system, raising central pulse pressure in the case of  $\beta$ -blockers.

The roles of arterial stiffness and wave reflections in the mechanisms of central BP reduction in subjects under antihypertensive drug therapy might be best demonstrated in the ASCOT and CAFE studies. In both trials, an ACE inhibitor, perindopril, was used with a calcium-channel blocker, amlodipine, and compared with an association of diuretic and  $\beta$ -blockers. In the ASCOT study, amlodipine-based treatments proved to be more effective than atenolol-based treatments for reducing cardiovascular events.<sup>65</sup> The CAFE study showed that the reduction in central systolic BP and pulse pressure was higher in the amlodipine- than in the atenolol-based treatment group, despite similar reductions in both pressures at the brachial level.<sup>66</sup>

The results of the REASON study (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study), which compared the antihypertensive effects of the very-low-dose combination of indapamide (0.625 mg) and perindopril

(2 mg) with the  $\beta$ -blocking agent atenolol (50 mg), showed a superior effect of the ACE inhibitor, perindopril, to atenolol in reducing both aortic PWV and wave reflections.<sup>60</sup> In the primary results of 1-year follow-up for the same diastolic BP reduction, perindopril/indapamide lowered brachial and carotid systolic BP and thus pulse pressure more than atenolol. This difference was significantly more pronounced for the carotid artery than for the brachial artery. Also, the wave-reflection changes resulting from the reduction of peripheral (arteriolar) reflection coefficients were the principal factor to consider in explaining the difference between atenolol and perindopril/indapamide with regard to systolic BP reduction.

Finally, the effect on central BP reduction by the ARB, olmesartan, in combination with either a calcium-channel blocker or a diuretic was compared in hypertensive patients (mean age, 68.4 years).<sup>67</sup> Though brachial systolic BP was similar between the 2 groups, the reduction in central systolic BP in the olmesartan/calcium-channel blocker group was significantly greater than in the olmesartan/diuretic group. In addition, aortic PWV was significantly more reduced in the olmesartan/calcium-channel blocker group. Again, these results suggest that the regulating capacity of arterial stiffness and wave reflections might differ among antihypertensive patients.

### Conclusions

Though arterial walls stiffen with age, it is not solely normative. Vascular aging is accelerated by the coexistence of cardiovascular risk factors and well confirmed to be a risk factor for cardiovascular disease. Various strategies, especially controlling hypertension, show benefit in attenuating vascular aging. Currently, reducing pulse pressure is the most effective strategy to prevent arterial stiffness and decrease wave reflections in elderly patients with systolic hypertension. In addition, the roles of newer therapies targeting at breaking collagen cross-links or preventing their formation should be investigated.

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