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<th><strong>Title</strong></th>
<th>Arterial stiffness in the young: Assessment, determinants, and implications</th>
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<tr>
<td><strong>Citation</strong></td>
<td>Korean Circulation Journal, 2010, v. 40 n. 4, p. 153-162</td>
</tr>
<tr>
<td><strong>Issued Date</strong></td>
<td>2010</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10722/123972">http://hdl.handle.net/10722/123972</a></td>
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Arterial stiffness describes the rigidity of the arterial wall. Its significance owes to its relationship with the pulsatile afterload presented to the left ventricle and its implications on ventricular-arterial coupling. In adults, the contention that arterial stiffness as a marker and risk factor for cardiovascular morbidity and mortality is gaining support. Noninvasive methods have increasingly been adopted in both the research and clinical arena to determine local, segmental, and systemic arterial stiffness in the young. With adoption of these noninvasive techniques for use in children and adolescents, the phenomenon and significance of arterial stiffening in the young is beginning to be unveiled. The list of childhood factors and conditions found to be associated with arterial stiffening has expanded rapidly over the last decade; these include traditional cardiovascular risk factors, prenatal growth restriction, vasculitides, vasculopathies associated with various syndromes, congenital heart disease, and several systemic diseases. The findings of arterial stiffening have functional implications on energetic efficiency, structure, and function of the left ventricle. Early identification of arterial dysfunction in childhood may provide a window for early intervention, although longitudinal studies are required to determine whether improvement of arterial function in normal and at-risk paediatric populations will be translated into clinical benefits. (Korean Circ J 2010;40:153-162)

KEY WORDS: Arteriosclerosis; Children.

Introduction

Arterial stiffness, in simple terms, describes the rigidity of the arterial wall. It is primarily determined by structural components of the arterial wall, vascular smooth muscle tone, and transmural distending pressure. Increasing evidence suggests a role of the endothelium in the regulation of arterial stiffness through the release of vasoactive mediators that affect smooth muscle tone.

The significance of arterial stiffness owes to its direct relationship with the characteristic impedance of the arterial system, which is the pulsatile component of the afterload that is presented to the left ventricle. Furthermore, arterial stiffening increases the velocity at which the pulse wave travels, resulting in an earlier return of the reflected wave from peripheral sites, and hence, suboptimal ventricular-arterial interaction. Given the relationships between arterial stiffness, vascular impedance and wave reflection, it is understandable that arterial stiffness may impact cardiovascular health.

The contention that arterial stiffness is a marker of vascular disease and a risk factor for cardiovascular morbidity and mortality, in adults, is gaining support. In adults, the association of increased arterial stiffness with various pathophysiological conditions has been extensively reviewed. Importantly, stiffness of central arteries, as assessed by the aortic pulse wave velocity (PWV) and carotid distensibility, has been shown to have an independent predictive value for cardiovascular events in the general adult population, in elderly, and in adults with hypertension, end-stage renal failure, and impaired glucose tolerance.

Noninvasive methods have been increasingly adopted in both the research and clinical arenas to determine systemic arterial stiffness, and these methods have sig-
nificantly increased the understanding of the pathophysiologica significance. With adoption of these non-invasive methodologies for use in children and adolescents, the phenomenon and significance of arterial stiffening in the young are beginning to unfold. The present article aims to provide an overview of the methods used to assess arterial stiffness in vivo and of the determinants and significance of arterial stiffness in children and adolescents.

Measurement of Arterial Stiffness In Vivo

Noninvasive methods are available for determination of 1) local or cross-sectional stiffness at a particular site in the artery, 2) regional stiffness along the length of an arterial segment, and 3) systemic or whole-body arterial stiffness.

Local arterial stiffness

Local arterial stiffness is ascertained by relating changes in arterial diameter or cross-sectional area to pressure changes at the site of interest. The commonly used indices for quantification of local arterial stiffness are summarized in Table 1.

For superficial arteries including the brachial, femoral, and carotid arteries, the diameter and diameter change from end-diastole to end-systole can be assessed by ultrasound (Fig. 1A) and echo-tracking techniques. Compared with two-dimensional ultrasound assessment, echo-tracking permits the tracking of displacement of the anterior and posterior arterial walls with a much higher precision. For deeper arteries, such as the aorta, magnetic resonance imaging and transesophageal echocardiography with acoustic quantification have been used to determine the change in arterial diameter during the cardiac cycle.

Ideally, local pressure should be measured at the site of diameter measurements. Applanation tonometry (Fig. 1B) allows noninvasive recording of the arterial pressure wave on the carotid and peripheral conduit arteries. The tonometer has the size of a pen, is hand-held and gently compressed against the underlying bone, thus flattening the artery slightly and equalizing the circumferential pressures. The recorded pressure waveform is almost identical to that obtained intra-arterially and can then be calibrated against the cuff mean and diastolic blood pressures of the brachial artery. Alternatively, the cuff brachial artery pulse pressure has also been commonly used for the calculation of local arterial stiffness indices. Amplification of pulse pressure along the arterial tree, however, constitutes a potential source of error.

Recently, tissue Doppler imaging and speckle tracking echocardiography have been used to assess arterial strain and strain rate as novel indices of cross-sectional arterial stiffness.

Regional arterial stiffness

Measuring the PWV over the segment of interest assesses stiffness along the length of an arterial segment or regional stiffness. PWV is the speed at which the forward pressure or flow wave is transmitted from the aorta through the arterial tree.

The Bramwell and Hill equation relates PWV to arterial distensibility: $\text{PWV} = \sqrt{\frac{\Delta P \cdot V}{\Delta V \cdot \rho}} = \frac{1}{\rho} \frac{\Delta P}{\Delta V}$, where $P$ is pressure, $V$ is volume, $\Delta P \cdot V/\Delta V$ represents volume elasticity, $\rho$ is density of blood, and $D$ is volume distensibility of the arterial segment. Hence, PWV is related inversely to arterial distensibility; in other words, the stiffer the artery, the faster the PWV. By providing an average stiffness of the arterial segment of interest, PWV may provide a better reflection of the general vascular health.

PWV is determined by dividing the distance of pulse travel, between two sites, by the transit time. As the pulse pressure and flow pulse propagate at the same velocity, the arterial pulse may be registered using pressure-sensitive transducers, an oscillometric device, and

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<th>Table 1. Commonly used indices of local or cross-sectional arterial stiffness</th>
<th>Definition</th>
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<tr>
<td>Peterson elastic modulus</td>
<td>Pressure change required for a given relative change in diameter (inverse of distensibility)</td>
<td>$\Delta P \cdot D/\Delta D$</td>
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<tr>
<td>Distensibility</td>
<td>Relative change in diameter during systole for a given pressure change</td>
<td>$D/(D \cdot \Delta P)$</td>
</tr>
<tr>
<td>Compliance</td>
<td>Absolute change in diameter during systole for a given pressure change</td>
<td>$\Delta D/\Delta P$</td>
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<td>Stiffness index ($\beta$)</td>
<td>Ratio of ln (systolic/diastolic pressure) to relative change to vessel diameter</td>
<td>$\ln (P_s/P_d)/(\Delta D/D)$</td>
</tr>
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D: diastolic diameter, $\Delta D$: difference in systolic and diastolic diameter, ln: natural logarithm, $\Delta P$: pressure, $P_s$: diastolic blood pressure, $P_d$: systolic blood pressure

![Fig. 1. Derivation of local arterial stiffness by measurement of (A) diameter changes in the cardiac cycle using two-dimensional ultrasound, and (B) arterial pressure using applanation tonometry.](image-url)
The distance along which the pulse travels is usually estimated by direct superficial measurement between the two pressure transducers or other devices used to register the pulse. Transit time is measured as the time delay between the feet of the proximal and distal pulse waves (Fig. 3). The foot of the pulse wave is used as it is relatively unaffected by wave reflections. A potential source of error is the need to use the nearest superficial arteries as a surrogate site for inaccessible central arteries, and the estimation of the actual distance between the recording sites using surface measurements. Despite these limitations, PWV is probably the most widely used technique for assessment of arterial stiffness.

**Systemic arterial stiffness**

Pulse contour analysis has been used to assess systemic or whole-body arterial stiffness noninvasively. One of the methods focuses on the diastolic pressure decay of the radial pulse contour obtained by tonometry. An algorithm is used to determine the best set of values for matching the diastolic contour to a multi-exponential waveform equation. Based on these values, the lumped compliance of the major arteries and that of the small peripheral arteries is estimated. However, the biologic relevance of the derived lumped compliance remains unclear.

The area method has also been used to determine systemic arterial compliance using the formula: compliance = $A / (\text{total vascular resistance} \times (P_{es} - P_{d}))$, where $A$ is area under the diastolic portion of the arterial pressure wave from end-systole to end-diastole, $P_{es}$ is end-systolic pressure, and $P_{d}$ is end-diastolic pressure. The pressure readings and waveform are obtained by applanation tonometry over the common carotid artery. The total vascular resistance is calculated as mean blood pressure divided by mean aortic blood flow, the latter obtained by a velocimeter positioned at the suprasternal notch. The area method nonetheless shares a similar concern as the aforementioned.

**Arterial Stiffening in the Young**

**Evolution with age**

Aortic, upper limb, and lower limb pulse wave velocities increase with age from child- to adulthood. Notwithstanding the influence of distending pressure on arterial stiffness, previous data did not suggest that the change in PWV with age is entirely due to differences in systemic blood pressure. With cyclical mechanical stress, fragmentation of the elastin fibres and transfer of stress to the much stiffer collagen fibres inevitably results in the progressive increase in vascular stiffness.

Furthermore, studies of developmental changes in arterial structure during childhood have demonstrated progressive increase in intimal and medial thickness after birth. Hence, the observed age-related increase in stiffness is likely related to progressive structural changes in the arterial wall during childhood. Interpretation of results obtained from paediatric populations at risk for arterial dysfunction should therefore take into account age-related evolution.
Cardiovascular risk factor

Traditional cardiovascular risk factors associated with arterial stiffening in childhood and are summarized in Table 2.

Prenatal growth restriction

The ‘fetal origins hypothesis’ proposes that cardiovascular disease originates through adaptation to an adverse environment in utero. These adaptations have been suggested to cause permanent alterations in cardiovascular structure and physiology through the process of programming. Indeed, there is evidence that individuals who are born small may be at risk for arterial dysfunction in childhood and adulthood.

In very low birth weight, premature infants, reduced aortic wall distensibility and whole-body compliance have been shown as early as the neonatal period. Other studies have demonstrated inverse relationships between systemic arterial stiffness and gestational age and birth weight standardized for gestational age. In fetuses with umbilical placental insufficiency, an increase in afterload has been shown to result in a decrease in aortic distensibility during the neonatal period. Furthermore, reduced compliance of the aorta and conduit arteries of the legs has been shown to occur in adults born small.

In monozygotic twins with twin-twin transfusion syndrome, the growth-restricted donor twin has been reported to have increased peripheral conduit arterial stiffness during infancy. Such vascular programming has been shown to be ameliorated, albeit not completely abolished, by intrauterine endoscopic laser ablation of placental anastomoses. Even in monozygotic twins without twin-twin transfusion syndrome, the twin with the lower birthweight has been found to have higher systolic blood pressure and pulse pressure in childhood.

The mechanism whereby low birth weight is associated with increased arterial stiffness in childhood remains unclear. The reported endothelial dysfunction in individuals born preterm and small-for-gestational age suggests that functional alteration of arterial tone may contribute to an increase in systemic arterial stiffness. Altered haemodynamics in intrauterine growth retardation, which result in preferential per-

Vasculitides

Vasculitis is the predominant feature in several childhood diseases. The acute inflammation and subsequent reparative process may lead to replacement of elastic tissue by fibrous scar, thereby potentially altering the mechanical properties of the vessels.

Kawasaki disease, a systemic vasculitis with predilection for children in the East, is the most commonly acquired heart disease in children in developed countries. Apart from the well-documented long-term structural alteration and functional disturbance of coronary arteries, systemic arterial dysfunction is increasingly documented. Indeed, concerns have been raised regarding the possibility of its predisposition to premature atherosclerosis in adulthood.

Increased stiffness of the carotid artery and brachial radial artery has been documented in the long-term follow-up of patients with a history of Kawasaki disease. Measurement of aortic input impedance during cardiac catheterization showed reduction in both characteristic impedance and total peripheral arterial compliance, regardless of the persistence of coronary artery aneurysms, suggesting an increase in both central and peripheral arterial stiffness. The magnitude of chronic low-grade inflammation, as reflected by elevated high-sensitivity C-reactive protein, in patients with coronary aneurysm formation has been associated positively with carotid arterial stiffness. Additionally, mannos-binding lectin, C-reactive protein, and tumour necrosis factor genotype polymorphisms have recently been found to exert modulating effects on long-term systemic arterial stiffness in Kawasaki patients.

In another type of childhood vasculitis, polyarteritis nodosa, the recurrent inflammatory cycles result in multiple stages comprised of acute fibrinoid necrosis and healing fibrotic lesions. While the chronic phenomenon, with recurrent episodes of inflammatory exacerbations, contrasts with the acute vasculitis in Kaw-
saki disease, stiffening of the peripheral conduit arterial stiffness and its amplification, during episodes of inflammatory exacerbation, are similarly found in polyarteritis nodosa.\textsuperscript{12)}

\textbf{Vasculopathies}

Abnormalities of the arterial vasculature have been described in Marfan and Williams syndromes and in association with a bicuspid aortic valve. Marfan syndrome is caused by a mutation in the gene that encodes fibrillin-1,\textsuperscript{88)} a matrix glycoprotein that is the principal constituent of microfibrils. On the other hand, haploinsufficiency of the elastin gene has been implicated in the arteriopathy of Williams syndrome.\textsuperscript{89)} Increased aortic stiffness is well documented in patients with Marfan syndrome, as shown by the decreased distensibility and increased stiffness index,\textsuperscript{90-97)} increased PWV,\textsuperscript{98} and decreased tissue Doppler-derived systolic and diastolic velocities of the aortic wall.\textsuperscript{99)} Importantly, aortic stiffness has been shown to be an independent predictor of progressive aortic dilation\textsuperscript{100,101)} and aortic dissection.\textsuperscript{101)} Beta-blocker therapy\textsuperscript{98} and angiotensin-converting enzyme inhibition\textsuperscript{102)} appear to reduce aortic stiffness, which may, in turn, slow aortic dilation and delay aortic root replacement.\textsuperscript{102)} Despite a biological basis for abnormal elastic fibres, results of studies exploring arterial elastic properties in patients with Williams syndrome are controversial.\textsuperscript{103-106)} In both children and adults,\textsuperscript{107)} an isolated bicuspid aortic valve is associated with progressive dilation of the ascending aorta and increased aortic stiffness.\textsuperscript{108,109)}

\textbf{Congenital heart disease}

In a variety of congenital heart lesions, medial abnormalities with elastic fibre fragmentation have been identified in intraoperative biopsies and necropsy aortic specimens.\textsuperscript{110)} These congenital heart lesions include tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus, complete transposition of the great arteries, coarctation of the aorta, double-outlet ventricles, and univentricular hearts.

In children and adolescents with tetralogy of Fallot, aortic stiffness has been shown to be increased and related to the aortic root dimensions.\textsuperscript{111)} Additional data suggest that there is preferential stiffening of the central, over peripheral, conduit arteries.\textsuperscript{112)} Importantly, the heart-femoral PWV has been found to be a significant size determinant of the sinotubular junction, suggesting that central arterial stiffening may contribute to progressive aortic root dilation in these patients.

In transposition of the great arteries, patients undergoing two-stage anatomic correction were found to have decreased distensibility of the neoaorta, and this is thought to be related to pulmonary arterial banding.\textsuperscript{113)} Nonetheless, even after one-stage arterial switch operation, impaired distensibility of the neoaorta has similarly been documented.\textsuperscript{114)} Recent studies documented an increased stiffness index of the carotid artery in patients both after atrial and arterial switch operations,\textsuperscript{115,116)} suggesting that impaired elastogenesis may be an intrinsic component of this congenital anomaly.

In the aortic segment proximal to the site of aortic coarctation, an increase in collagen and decrease in smooth muscle content have been described.\textsuperscript{117)} Functionally, distensibility of the aortic arch has been shown to be significantly lower than that of the distal thoracic aorta.\textsuperscript{118)} The importance of early coarctation repair on possible prevention of late vascular dysfunction is highlighted by the inverse relationships found between age at repair and stiffness and vascular reactivity of the precoarctation arterial segments.\textsuperscript{118-120} Interestingly, the results of a recent study suggest that impaired elastic properties of the prestenotic aorta may be a primary abnormality as evidenced by an increased ascending aortic stiffness index, even preoperatively, in neonates with coarctation.\textsuperscript{121)}

\textbf{Systemic childhood diseases}

Apart from diseases of the heart and blood vessels, several chronic systemic diseases in childhood have been found to be associated with arterial stiffening (Table 3).\textsuperscript{122-129)}

\textbf{Functional Implications on Cardiac Performance}

Ventricular afterload is increased in the presence of systemic arterial stiffening. To generate the same stroke

\textbf{Table 3. Systemic childhood conditions associated with arterial stiffening}

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<th>Risk factor</th>
<th>Arteries involved</th>
<th>Reference</th>
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<td>Juvenile rheumatoid arthritis</td>
<td>↑ pulse wave velocity and ↓ distensibility of the aorta</td>
<td>122</td>
</tr>
<tr>
<td>Systemic lupus erythematous</td>
<td>↑ carotid arterial stiffness</td>
<td>123</td>
</tr>
<tr>
<td>Chronic infection with human immunodeficiency virus</td>
<td>↑ elastic modulus of the carotid arterial wall</td>
<td>124</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>↑ carotid-femoral pulse wave velocity and augmentation index</td>
<td>125, 126</td>
</tr>
<tr>
<td>(↑ carotid arterial stiffness even after renal transplantation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-thalassaemia major</td>
<td>↑ stiffness of the carotid artery, brachioradial artery, and aorta</td>
<td>127, 128</td>
</tr>
<tr>
<td>Primary snoring</td>
<td>↑ brachioradial arterial stiffness</td>
<td>129</td>
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volume against a stiffened arterial tree, with increased afterload, the systemic ventricle has to generate a higher end-systolic pressure at the expense of greater myocardial oxygen consumption.

Structural adaptation of the left ventricle to increased afterload is also evident in the presence of arterial stiffening. In an otherwise healthy population of adults, measures of arterial stiffness including elastic modulus, distensibility, and PWV have been shown to be significant determinants of left ventricular mass.\(^1\)

Arterial stiffening is also associated with alteration of phasic coronary flow pattern.\(^2\) Early return of the reflected pressure wave, due to a faster PWV, augments central systolic pressure and lowers diastolic coronary perfusion pressure.

The increased myocardial oxygen consumption, left ventricular hypertrophy, and decreased diastolic coronary perfusion pressure predispose the conditions of subendocardial ischemia and interstitial fibrosis, which in turn can impair myocardial relaxation and reduce ventricular compliance.\(^3\)\(^4\)\(^5\) Indeed, associations between arterial stiffness and left ventricular diastolic dysfunction in adults with hypertension\(^6\)\(^7\)\(^8\) and diabetes mellitus\(^9\)\(^10\)\(^11\)\(^12\)\(^13\) are recognized. Associations between arterial stiffening and left ventricular systolic function in adults with\(^14\) and without\(^15\) coronary artery disease have also been found.

### Clinical implications on management

Early identification of arterial dysfunction in childhood may provide a window for early intervention. Amelioration of endothelial dysfunction may reduce arterial stiffness through the lowering of smooth muscle tone. The potential beneficial effects on endothelial function of folic acid in children with renal failure,\(^16\)\(^17\)\(^18\)\(^19\)\(^20\) antioxidants and statins in those with familial hypercholesterolemia,\(^21\)\(^22\)\(^23\) vitamin C in those with Kawasaki disease,\(^24\)\(^25\) and exercise training in obese children\(^26\)\(^27\)\(^28\) have been reported. In patients with Marfan syndrome, beta-blocker therapy\(^29\) and angiotensin-converting enzyme inhibition\(^30\) appear to reduce aortic stiffness.

Lifestyle modification early in life may prevent premature stiffening of arteries. In this regard, there is evidence to suggest a beneficial impact on arterial stiffness by sodium restriction,\(^31\)\(^32\) regular exercise,\(^33\) intake of fish oil\(^34\)\(^35\) and isoflavone,\(^36\) and smoking cessation.\(^37\) Longitudinal studies are, however, required to determine whether improvement of arterial function in the young will be translated into clinical benefits in adulthood.

### Conclusions

With availability of noninvasive technologies for determination of arterial stiffness in children, the significance of the phenomenon of arterial stiffening in the young is becoming better understood. Importantly, even in children and adolescents, accumulating evidence suggests that clinical conditions associated with abnormal functioning of the arterial system may have long-term clinical implications. Further studies to elucidate the underlying mechanisms of arterial stiffening in the young are warranted. Additionally, longitudinal studies are required to clarify whether systemic arterial stiffening tracks from child- to adulthood and whether early implementation of strategies to reduce arterial stiffness may have an impact on long-term cardiovascular health in both healthy and at-risk paediatric populations.

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