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Occasional Survey

Arterial Stiffness in Children and Teenagers: An Emerging Cardiovascular Risk Factor

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Abstract Arterial stiffness, the rigidity of the arterial wall, owes its significance to a direct relationship with impedance of the arterial system, and hence the left ventricular afterload. In adults, arterial stiffness has been considered as a marker of vascular disease and is emerging as an independent cardiovascular risk factor. There is accumulating evidence that this may also be true in children. Several paediatric clinical entities may affect normal functioning of the arterial system and may have an impact on long term cardiovascular health. Both prenatal and postnatal influences affect the age-dependent evolution of arterial stiffness. The prenatal influence of reduced fetal growth is illustrated by the findings of increased arterial stiffness in individuals born small and the growth-restricted donor twins in twin-twin transfusion syndrome. Postnatal structural alteration of arteries secondary to childhood vasculitides increases peripheral conduit arterial stiffness significantly. Furthermore, the magnitude of vascular inflammation during the acute phase may have important bearings on late arterial stiffening. Functional alterations of the arteries may also increase arterial stiffness. Endothelial dysfunction, documented in children with familial hypercholesterolaemia, obesity and beta-thalassaemia major, has a direct relationship with arterial stiffening. Alternatively, enhanced sympathetic tone, as might occur in childhood sleep-related disorders, may increase arterial stiffness. With the availability of noninvasive techniques for the determination of arterial stiffness in children, longitudinal studies incorporating this measurement may unveil its prognostic value in the paediatric at-risk population.

Key words Arterial stiffness; Cardiovascular risk factor; Children

Introduction

The mechanical properties of the arterial system have been of continuing interest to physiologists and biomedical engineers. In the last decade, the clinical relevance of arterial stiffness has increasingly been recognised,[1-3] in particular the association between arterial stiffening and cardiovascular disease in adults. Arterial stiffness, in simple terms, describes the rigidity of the arterial wall, which is determined primarily by the structural component, primarily elastin and collagen, and smooth muscle tone of the arterial wall and dependent on the distending pressure.[4] Its significance owes to its direct relationship with characteristic impedance of the arterial system, and hence 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 earlier return of the reflected wave from peripheral sites and suboptimal ventriculo-arterial interaction. Given the relationships between arterial stiffness, vascular impedance and wave reflection, it is perhaps not surprising that arterial stiffness may impact on cardiovascular health.

There is compelling evidence that increased aortic

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stiffness is associated with increased cardiovascular mortality and morbidity in adults with hypertension and end stage renal disease.[5-7] Indeed, the contention that arterial stiffness is a marker of vascular disease and a risk for cardiovascular mortality in adults is gaining support. In children and teenagers, there is accumulating evidence that several clinical entities may affect normal functioning of the arterial system and may hence have an impact on long-term cardiovascular health. The present article aims to provide an overview of the methods used to assess arterial stiffness in vivo and the determinants of arterial stiffness in children and teenagers.

Quantification and Assessment of Arterial Stiffness

Table 1 summarises the indices commonly used for quantification of arterial stiffness. The indices may broadly be categorised into those that describe local, regional, and systemic arterial stiffness, respectively.

Local Arterial Stiffness

Local arterial stiffness of superficial arteries can be determined by assessing the pressure and diameter changes at the site of interest. The arterial diameter and diameter change during the cardiac cycle can be assessed by ultrasound and echo-tracking techniques. These techniques are mainly used for assessing the stiffness of the larger and more accessible arteries, namely the brachial, femoral and carotid arteries. For measurement of the diameter and distension of deeper arteries as the aorta, cine magnetic resonance imaging[8] and acoustic quantification[9] have been used.

Applanation tonometry allows noninvasive recording of the arterial pressure waveform and magnitude in both the central and peripheral arteries.[10] The tonometer is the size of a pen and is hand-held and gently compressed against the underlying bone, thus flattening the artery slightly and equalising the circumferential pressures. The recorded pressure waveform is almost identical to that obtained intra-arterially.[11]

By relating the pressure changes to the diameter changes, arterial stiffness can be expressed as elastic modulus, distensibility, and stiffness index (Table 1). While new high-resolution imaging modalities increase the accuracy in the assessment of the artery diameter change during the cardiac cycle, determination of the corresponding pressure change might be problematic. Problems include amplification of the pressure pulse along the arterial tree[12] and inaccuracy of the cuff sphygmomanometer system.[13] Although the pulse pressure should ideally be measured at the site of the diameter measurements, a representative arterial pulse pressure may not always be obtainable non-invasively.

Table 1 Indices of arterial stiffness

Term	Definition
Elastic modulus	The pressure change required for theoretical 100% stretch from resting diameter $(\Delta P \cdot D) / \Delta D$ (mmHg)
Arterial distensibility	Relative change in diameter (or area) for a given pressure change; inverse of elastic modulus $\Delta D / (\Delta P \cdot D)$ ($mmHg^{-1}$)
Stiffness index (β)	Ratio of logarithm (systolic / diastolic pressures) to (relative change in diameter) $\beta = \frac{\ln (P_s / P_d)}{(D_s - D_d) / D_d}$
Pulse wave velocity	Velocity of travel of the pulse along an arterial segment Distance / Δt (cm/s)
Capacitative compliance (Large artery elasticity index)	Relationship between pressure change and volume change in the arteries during the exponential component of diastolic pressure decay $\Delta V / \Delta P$ (cm^3/mmHg)
Oscillatory compliance (Small artery elasticity index)	Relationship between oscillating pressure change and oscillating volume change around the exponential pressure decay during diastole $\Delta V / \Delta P$ (cm^3/mmHg)

d, diastolic; D, diameter; P, pressure; s, systolic; t, time; V, volume

Regional (Segmental) Arterial Stiffness

Arterial stiffness of an arterial segment, or regional stiffness, is assessed by measuring the pulse wave velocity (PWV) over the segment of interest. Pulse wave velocity is the speed at which the forward pressure or flow wave is transmitted from the aorta through the vascular tree. Pulse wave velocity is related inversely to arterial distensibility; in other words, the stiffer the artery, the faster the PWV.

Pulse wave velocity is calculated by measuring the time taken for the arterial waveform to pass between two points, and involves taking readings from the two sites simultaneously, or by gating separate recordings to a fixed point in the cardiac cycle, usually the R wave of the electrocardiogram. Various methods have been used, both invasive and non-invasive, which can be applied to either pressure or flow waves.

While it is not possible to determine the local elastic property of the artery, PWV provides the average stiffness throughout the arterial segment of interest and may therefore provide a more general assessment of vascular health.[14] Furthermore, it has the advantage of not requiring an accurate record of the pressure wave in the segment of interest. Problems with this technique, however, include the need to use of the nearest superficial arteries as a surrogate site for inaccessibility central arteries and the estimation of the actual distance between the recording sites using surface measurements. Despite these limitations, pulse wave velocity is probably the most widely used technique for assessment of arterial stiffness.[12,15]

Systemic Arterial Stiffness

Pulse contour analysis has been used to assess the estimate the systemic arterial stiffness non-invasively.[13,16] This technique concentrates exclusively 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 portion of the measured beat to a multiexponential waveform equation. Based on these values, the lumped compliance of the major arteries (C_1) and that of the small peripheral arteries (C_2) are estimated.

The concept of whole-body compliance, or systemic arterial stiffness, as a physiological variable is, however, problematic. The heterogeneity among large and small arteries in terms of their elastic properties is significant. The complex matrix of the arterial circulation, with diverse properties of the parallel circuits and of the proximal and distal vessels within each circuit, casts doubt on the biologic relevance of indices of lumped compliance. Furthermore, the assertions that C_1 represent proximal, or large vessel compliance and that C_2 represents distal, or small-vessel, compliance are based entirely on a model construct that has not been validated.

Determinants of Arterial Stiffness in Children and Teenagers

With the availability of the aforementioned noninvasive techniques, significant determinants of central and peripheral conduit arterial stiffness in children and teenagers have been defined. Furthermore, there is accumulating evidence of arterial stiffening in several paediatric clinical entities that may have an impact on long-term cardiovascular health.

Normal Evolution

In a cohort of 480 Chinese subjects aged 3 to 89 years, Avolio et al[17] reported progressive increase in aortic, upper limb and lower limb PWV, measured by transcutaneous Doppler technique, with age. Age-dependent increase in brachio-radial arterial PWV is similarly demonstrated in a cohort of children and teenagers aged 6 to 18 years using a novel photoplethysmographic technique.[18] Using the area under the ascending aortic pressure-time curve to determine the total stiffness of the arterial tree and assuming a two-element Windkessel model,[19] Senzaki et al[20] demonstrated a nonlinear increase in the total arterial stiffness in children aged 6 months to 20 years. Although Laogun and Gosling[21] reported a nadir of arterial stiffness at around 10 years of age, their findings are not replicated in subsequent studies.[17,18,20,22]

Notwithstanding the influence of the distending pressure on arterial stiffness, previous findings did not suggest that the change in PWV with age is entirely due to differences in systemic blood pressure.[17,18] Rather, the gradual increase in arterial stiffness with age is probably related to progressive medial degeneration.[17] The rate of elastin synthesis increases to a maximum in the perinatal period and falls rapidly thereafter.[23] With the cyclic mechanical stress, fragmentation of the elastin fibres and transfer of the stress to the much stiffer collagen fibres inevitably result in progressive increase in vascular stiffness.[24] Furthermore, studies of developmental changes in arterial structure during childhood have demonstrated progressive increase in intimal and medial thickness after birth.[25] Hence, the observed age-related increase in stiffness is likely a reflection of structural changes in the arterial wall during

childhood. Interpretation of results obtained from paediatric subjects potentially with arterial dysfunction should therefore take into account of the age-related evolution.

Prenatal Growth Restriction

It has been more than a decade since the first report of associations between low birth weight and increased risk of cardiovascular disease.[26] These findings, having been replicated in a number of studies,[27-29] have led to the 'fetal origins hypothesis'[30] which states that cardiovascular disease originates through adaptation to an adverse environment in utero. These adaptations have been proposed to cause permanent alterations of cardiovascular structure and physiology through the process of programming. Nonetheless, the mechanisms that underlie the link between reduced fetal growth and increased cardiovascular risk remain speculative.

There is evidence that individuals who are born small are at risk of vascular dysfunction. Arterial endothelial dysfunction has been demonstrated in term infants,[31] children[32] and young adults[33] with low birthweight. Furthermore, reduced compliance of the aorta and conduit arteries of legs has been shown to occur in adults born small.[3] One of the proposed mechanisms is the impairment of synthesis of elastin in the arterial wall, which leads to arterial stiffening and accentuation of systolic afterload of the left heart.[24]

The cardiovascular risk for individuals who are born small as a result of prematurity is controversial.[34-36] Irving et al[34] reported an increase in systolic blood pressure and fasting glucose in a cohort of 34 young adults born prematurely, regardless of whether or not they have intrauterine growth retardation. Singhal et al,[35] however, found that only individuals who had been preterm babies with intrauterine growth retardation have evidence of arterial endothelial dysfunction, as reflected by significantly less flow-mediated dilation. Our recent study similarly suggests that it is this group of subjects who are predisposed to increased systemic arterial stiffness and higher blood pressure.[36] On the other hand, children whose birth weight is appropriate for gestation are not predisposed to such cardiovascular risk factors, regardless of the gestational age. Indeed, in this study, the birthweight standardised for gestational age is negatively correlated with and is a significant determinant of arterial stiffness.

In monozygotic twins with twin-twin transfusion syndrome, the growth-restricted donor twin provides a unique model for studying the effects of differing volume load and increased placental resistance on the developing cardiovascular systems in two genetically identical individuals. Indeed, studies have shown that the peripheral conduit arterial stiffness is increased during infancy in the donor twins.[37] Such vascular programming has been shown to be ameliorated, albeit not completely abolished, by intrauterine endoscopic laser ablation of placental anastomoses to resemble that seen in dichorionic twins.[38]

The mechanism whereby discordance between birth weight and gestational age leads to an increase in arterial stiffness in children remains unclear. Given the critical role of endothelium in the control of vascular tone,[39] the reported impairment of endothelial function in individuals born preterm and small-for-gestational age[35] suggests that functional alteration of arterial tone may contribute to an increase in systemic arterial stiffness. In children born at term, leanness at birth has been reported to correlate with the lowest endothelium-dependent microvascular responses and the highest carotid stiffness indices.[40] Altered haemodynamics in intrauterine growth retardation, resulting in preferential perfusion of upper part of body[41] may affect the mechanical properties of the large arteries concerned. Thus, selective atherosclerotic degeneration of the carotid arteries in elderly people has been demonstrated to be more severe in those with the lowest birth weight.[42] In the donor twins in twin-twin transfusion syndrome, the superimposed circulatory imbalance probably acts synergistically with growth restriction to cause the vascular programming, although the exact mechanism remains to be defined.[37]

Childhood 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,[43] thereby potentially altering the mechanical properties of the vessels.[44]

Kawasaki disease, a systemic vasculitis with predilection for Oriental children, is presently the commonest cause of acquired heart disease in children in developed countries. The sequelae of inflammation involving coronary and other medium-sized muscular arteries in the acute phase of Kawasaki disease have been well documented.[45-47] Similarly, long-term structural and functional disturbances of coronary arteries have also been described.[45-48] Importantly, even at the sites of regressed coronary aneurysms, coronary arterial intimal thickening[48] and stiffening[46] were noted in the long-term.

There is increasing evidence of an impact of acute diffuse vasculitis in Kawasaki disease on long-term systemic arterial function. Indeed, concerns have been raised

regarding the possibility of its predisposition to premature atherosclerosis in adulthood.[45,49-52] Abnormalities of brachial arterial endothelial dysfunction have been demonstrated in patients, even in those without early coronary artery involvement, studied at a median of 11 years after the acute illness.[53] Noto et al[54] showed an increase in carotid arterial stiffness and intima media thickness in patients with coronary aneurysms. Our group has further demonstrated stiffening of the peripheral conduit arteries and proatherogenic alteration of the lipid profile not only in patients with coronary aneurysms, but also in those without.[55]

Recent studies demonstrated significant elevation of serum high sensitivity-CRP levels in children and adolescents with a history of Kawasaki disease complicated by coronary aneurysm formation.[56,57] Furthermore, the data suggest a positive relationship between CRP level and carotid artery stiffness.[56] There is hence evidence to suggest that alteration of arterial function may be related in part to chronic low-grade inflammation that continues after the acute phase of Kawasaki disease. Indeed, histological examination revealed extensive fibrointimal thickening and infiltration of lymphocytes and plasma cells in the coronary arterial walls in fatal cases of Kawasaki disease occurring years after apparent resolution of vascular inflammation and in the absence of early detectable coronary artery abnormalities.[58]

Recently, we demonstrated significant induction of monocyte chemoattractant protein-1 (MCP1), chemokine receptor CCR2 and inducible nitric oxide synthase (iNOS) expression in THP-1 macrophages in vitro by the serum of children with a history of Kawasaki disease.[59] The serum from patients with coronary aneurysms, as compared to that from patients without coronary complications, was found to induce significantly greater expression of these genes. These findings provide the first in vitro evidence that arterial dysfunction and predisposition to premature atherosclerosis in patients after Kawasaki disease may in part be related to chronic activation of the MCP-1/CCR2 pathway and iNOS in vivo.

In another type of childhood vasculitis, polyarteritis nodosa, the recurrent inflammatory cycles result in multiple stages comprising acute fibrinoid necrosis and healing fibrotic lesions. While the chronic phenomenon with recurrent episodes of inflammatory exacerbations contrasts with the acute vasculitis in Kawasaki disease, stiffening of the peripheral conduit arterial stiffness and its amplification during episodes of inflammatory exacerbation are similarly found in polyarteritis nodosa.[18]

Systemic Childhood Diseases with Vascular Involvement

Arterial stiffness is determined by the structural component of the arterial wall, the smooth muscle tone and the arterial distending pressure. Cardiovascular risk factors and systemic diseases in childhood that affect arterial structure or vasomotor tone may therefore potentially affect systemic arterial stiffness.

Arterial stiffening has been documented in several adult diseases that are themselves also associated with increased cardiovascular risk, including hypertension, diabetes mellitis, hypercholesterolaemia and end-stage renal failure.[60] In children, severe obesity has also been shown to be associated with increased carotid arterial wall stiffness and brachial arterial endothelial dysfunction.[61] The risk factors implicated for these arterial changes include low apolipoprotein A-1, insulin resistance, and android fat distribution. It is also interesting to note that low grade inflammation, as determined by serum hs-CRP, is evident in obese juveniles.[62] The increased carotid intima media thickness in these individuals argues for a contribution of low grade inflammation to early atherosclerotic vessel injury in obese children. In a population-based study, significant inverse relationships were demonstrated between low-density lipoprotein cholesterol and apolipoprotein B and brachial arterial distensibility,[63] suggesting the possibility that cholesterol levels in the general population during childhood may already be relevant to the development of vascular disease. In children with familial hypercholesterolemia, increased stiffness of the comon carotid artery wall has also been shown to occur independent of systemic blood pressure.[64]

Iron-overloading in patients with beta-thalassaemia major results in alterations of arterial structures with disruption of elastic tissue and calcification.[65,66] Functional disturbances of human vascular endothelial cell when being incubated with thalassaemic serum has further been demonstrated in vitro.[67] We have previously shown that systemic arterial endothelial dysfunction and increased arterial stiffness in patients with beta-thalassaemia major.[68] Importantly, these phenomena occur in the absence of cardiac dysfunction that is known to alter arterial endothelial function and vascular tone.[69] Stiffness of both carotid and brachial-radial arteries were found to be inversely related to the magnitude of flow-mediation dilation, a measure of endothelial function, in our patients. This corroborates with findings of previous studies that demonstrated a critical role of endothelium in the control of vascular tone.[39,69] The findings of this study further support the view of a multi-factorial aetiology of left ventricular failure in patients with

beta-thalassaemia major.[70] Thus, apart from myocardial iron deposition,[70] myocarditis[71] and immunogenetic profile,[72] arterial dysfunction may also be contributory.

Sleep-related disorders, which are common in children, may also affect arterial function. Previous studies in children and adults suggest associations between obstructive sleep apnoea and hypertension.[73,74] While associations between obstructed sleep apnoea, the extreme of the spectrum of sleep-disordered breathing, and cardiovascular morbidities have been reported extensively,[73,75-78] relationship between snoring and cardiovascular complications remains controversial.[79-84] The paediatric population might be a better cohort for clearer definition of the issue due to less confounding influences. We have indeed shown that children with primary snoring have significantly higher daytime systemic BP and increased arterial stiffness, even after adjustment for the body mass index.[85] While the mechanism underlying the observed increase in systemic blood pressure and conduit arterial stiffness remains speculative, an increase in vasoconstrictors and an enhanced sympathetic tone,[82-84,86] proposed mechanisms underlying development of hypertension in adults with sleep-related disorders, might also be operative in children with sleep-related disorders.

Future Research Directions

With the availability of noninvasive technology for determination of arterial stiffness in children, longitudinal studies incorporating the measurement of arterial stiffness may unveil its prognostic value in these paediatric at-risk groups. Nonetheless, the typical clinical end points in studies of cardiovascular disease in adults rarely occur in paediatric patients. Surrogate end-points, as carotid intima-media thickness[87] and left ventricular hypertrophy,[88] that are known to be linked to manifestations of cardiovascular disease in adults may have to be used.[89] While the data in the literature support the speculations that disturbance of arterial elastic properties in the paediatric population is likely to be due to structural and function alterations of the arteries, the underlying mechanisms require further clarification. The results of studies on mechanisms would have important implications on novel treatment approaches,[90,91] that might prove effective in reducing arterial stiffness and its clinical consequences.

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