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Review Article

Utility of arterial stiffness assessment in children

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Abstract Atherosclerotic cardiovascular disease is a leading cause of death and disability worldwide, and the atherosclerotic process begins in childhood. Prevention or containment of risk factors that accelerate atherosclerosis can delay the development of atherosclerotic cardiovascular disease. Although current recommendations are to periodically screen for commonly prevailing risk factors for atherosclerosis in children, a single test that could quantify the cumulative effect of all risk factors on the vasculature, thus assessing arterial health, would be helpful in further stratifying risk. Measurement of pulse wave velocity and assessment of augmentation index – measures of arterial stiffness – are easy-to-use, non-invasive methods of examining arterial health. Various studies have assessed pulse wave velocity and augmentation index in children with commonly occurring conditions including obesity, hypertension, insulin resistance, diabetes mellitus, dyslipidaemia, physical inactivity, chronic kidney disease, CHD and acquired heart diseases, and in children who were born premature or small for gestational age. This article summarises pulse wave velocity and augmentation index assessments and the effects of commonly prevailing chronic conditions on arterial health in children. In addition, currently available reference values for pulse wave velocity and augmentation index in healthy children are included. Further research to establish widely applicable normative values and the effect of lifestyle and pharmacological interventions on arterial health in children is needed.

Keywords: Pulse wave velocity; augmentation index; children; atherosclerosis

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Background

Cardiovascular disease is a leading cause of death and disability in the United States, accounting for one out of every three deaths.[1] Although clinical manifestations usually present in adulthood, the atherosclerotic process begins in the first decade of life. Pathologically, the process begins with accumulation of cholesterol and lipids in the intimal layer of the arterial wall, which stimulates inflammation. There is ensuing deposition of calcium and collagen, as well as decreased elastin in the wall, resulting in arterial stiffening over time. Comorbid conditions such as hypertension, diabetes, obesity, or dyslipidaemia accelerate these processes through wall shear stress, advanced glycation end products, or lipid deposition.[2]

Accelerated atherosclerosis can be contained by preventing the onset of or by modifying risk factors such as obesity, hypertension, insulin resistance, dyslipidaemia, cigarette smoke exposure, and physical inactivity.[3] Such risk factors often cluster in children. Risk factor screening has been the primary mechanism for identifying children at risk for atherosclerosis. The effects of these risk factors on the vasculature can, however, vary based on the severity of the risk factor, length of exposure to the risk, interaction between risk factors, and interaction with known or unknown genetic and environmental predispositions. Thus, a single test that could quantify the effects of risk factors on the vasculature could serve as a robust tool for assessing arterial health in children.

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Currently, there are various non-invasive tests that assess vascular health by examining arterial structure and function. These include arterial endothelial functional assessments such as flow-mediated vasodilatation[4], structural assessments such as measurement of carotid artery intima–media thickness[5], or measurement of arterial stiffness and distensibility.[6] Flow-mediated vasodilatation, a measure of vascular endothelial function, has been shown to be deranged in children in a variety of conditions such as obesity[7], hypertension[8], type 1 diabetes[9], dyslipidaemia[10], and chronic renal disease.[11] Studies have shown that the presence of cardiovascular risk factors in childhood is also associated with structural changes in the arteries measured as increased carotid artery intima–media thickness during childhood[12,13] and in young adults.[14] It is intuitive to assume that a damaged vascular endothelium would first alter vascular function and then progress to deranged vascular tone and structure. However, large-scale, cross-sectional and longitudinal studies comparing functional and structural arterial assessments using uniform methodology are not available in children, thus limiting our understanding of evolution of vascular disease in children.

Assessments of flow-mediated vasodilatation and carotid artery intima–media thickness require expensive equipment, a high level of technical expertise[15], and lack standard protocols for data acquisition and analysis[16], thus limiting their application. Arterial stiffness assessment can be performed without imaging equipment and with minimal training, has been widely studied in adults, and is easily reproducible. Such non-invasive and non-imaging techniques that measure arterial stiffness – pulse wave velocity and assessment of augmentation index – have recently gained traction as methods of assessing arterial health in children. In adults, pulse wave velocity and augmentation index are predictors of both cardiovascular events and all-cause mortality.[17,18–20,21] Studies in children have also described changes in pulse wave velocity and augmentation index in various, commonly prevailing chronic conditions in children. In this article, we describe pulse wave velocity and augmentation index measurements, methodology, and their relevance in commonly occurring chronic conditions in children.

Part I

What is pulse wave velocity?

As the left ventricle contracts, it generates a pulse wave that begins at the ascending aorta and gets propagated forward by the elastic properties of the vessel wall. The velocity of propagation of the pulse wave can be measured as the distance travelled divided by the time taken to travel that distance:

$$\text{Pulse wave velocity} = \Delta L \div \Delta t$$

where ΔL is the distance travelled by pulse wave and Δt the time taken to travel this distance.

Stiffening of arteries or alteration of vascular tone owing to neurohumoral factors can lead to less elastic recoil, thereby increasing pulse wave velocity (Fig 1).

How is pulse wave velocity measured?

Pulse wave velocity can be measured between any two branches of the arterial tree. Central pulse wave velocity measures pulse wave velocity between larger arteries – for example, carotid–femoral – and peripheral pulse wave velocity measures pulse wave velocity of the more distal arterial segments – for example, brachial–radial or femoro–posterior tibial[22] (Fig 2).

Carotid–femoral pulse wave velocity. Carotid–femoral pulse wave velocity is most commonly used to assess pulse wave velocity (Fig 3). Waveforms of the right common carotid artery and the right femoral artery are obtained using non-invasive techniques. Transit time (Δt), the time for the pulse wave to travel from T_1 and T_2, is measured with one of two methods: the electrocardiogram-gated method or the foot-to-foot method. The electrocardiogram-gated method measures the time lapse between R wave of the electrocardiogram and the foot of the carotid artery waveform, and subtracts this value from the time lapse of the R wave and the foot of the femoral artery waveform. The foot-to-foot method uses simultaneously measured carotid and femoral artery waveforms; the lapsed time between the "feet" of these waveforms is the time taken for the pulse to travel the distance and serves as the denominator of the pulse wave velocity equation. The length (ΔL) that is travelled by the pulse wave is estimated by measuring the surface distance between the two recording sites. Pulse wave velocity is expressed as metres/second.[22]

Techniques to obtain pulse wave velocity. Several non-invasive techniques are available to measure pulse wave velocity. In applanation tonometry, pressure is applied to distort or applanate (flatten) the artery using a special probe, creating a signal that approximates arterial pressure. This method is considered the gold standard for measuring pulse wave velocity.[15] However, this technique requires a skilled operator and can be difficult to measure in obese or fidgety children. Oscillometric devices use a specialised blood pressure cuff to detect "oscillations" in pressure. This method is gaining traction as an easier and less operator-dependent method to assess pulse wave velocity.[23] Other less used techniques

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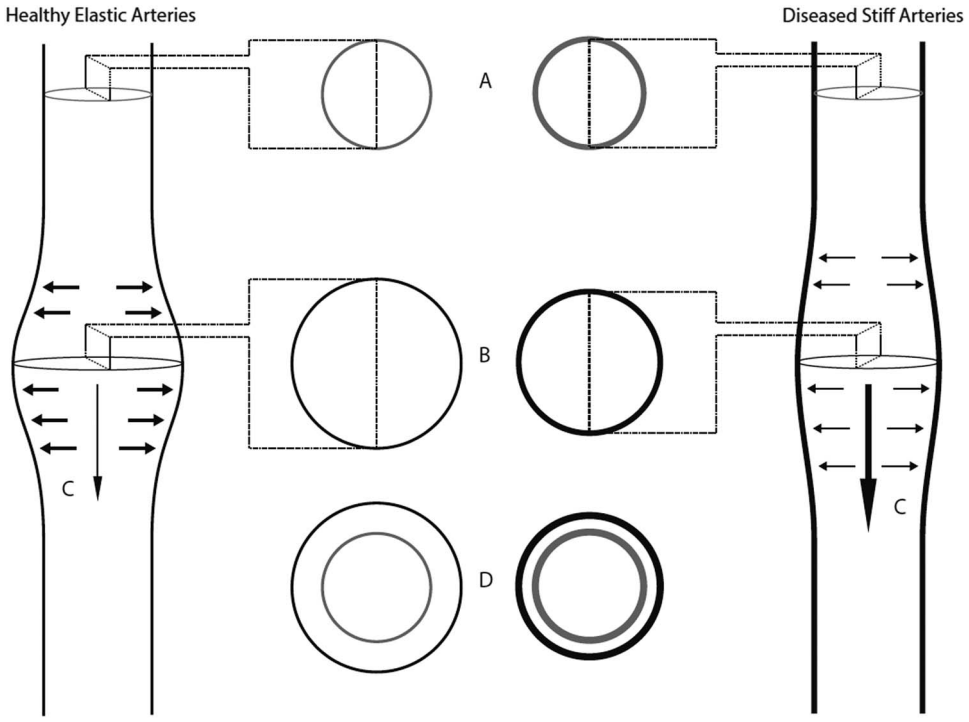

Figure 1.
Pulse wave velocity physiology.
A- The lumens of a healthy elastic artery (left panel) and a diseased stiff artery (right panel) during diastole.
B- During systole, as the pulse wave travels through a healthy elastic artery, there is an increase in pressure within the artery, which exerts a force on the artery wall and leads to an increase in volume. Elastic arteries are more distensible, and thus have a greater increase in volume for a given amount of pressure than stiff arteries.
C- The pulse wave travels slower in elastic arteries when compared to stiff arteries, as elastic arteries are more distensible.
D- Diseased arteries have decreased distensibility.

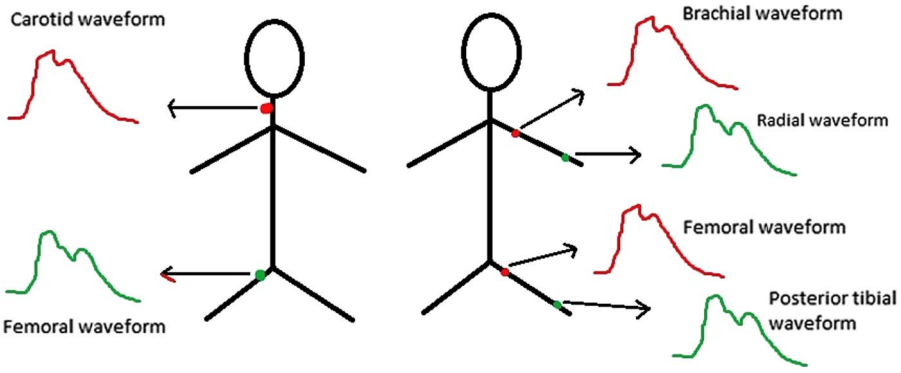

Figure 2.
Some examples of central (left panel) and peripheral (right panel) pulse wave velocity measurements.

include magnetic resonance imaging[24] and Doppler ultrasound.[25] These require specialised imaging equipment and technical personnel training.

What is augmentation index?

Augmentation index is another measure of arterial stiffness that is frequently used alongside pulse wave velocity.[22] As the pulse wave is transmitted through the arteries, it encounters resistance from multiple branch points, smaller arteries, and peripheral vascular beds. These reflections summate into a retrograde waveform. In an elastic vasculature, the reflected wave returns to the aortic root during diastole. The reflected wave returns sooner as the arteries stiffen, and the pressure in the aortic root is composed of both the

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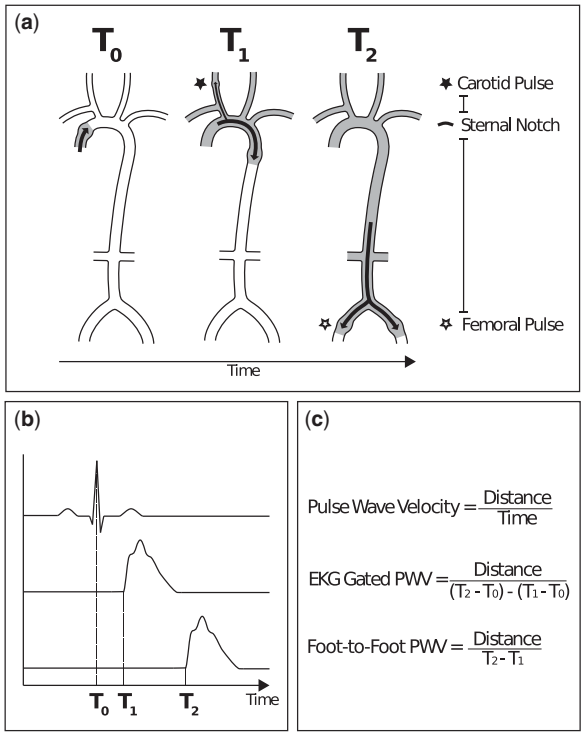

Figure 3.
Carotid–femoral pulse wave velocity.
A- At systole (T0), contraction of the heart leads to propagation of the pulse wave.
At T1, the pulse wave reaches the right common carotid artery, where it can be measured.
At T2, the pulse wave reaches the right common femoral artery, where it can be measured.
The distance between pulse points (to *) can be measured by directly measuring the path length that the pulse wave travels.*
B- A graphical depiction of the timing of systole, measured with electrocardiogram (T0), the right common carotid artery waveform (T1), and the right common femoral artery waveform (T2).
C- The denominator of the pulse wave velocity equation, the time for the pulse wave to travel from T1 and T2, is usually measured with one of two methods: the electrocardiogram-gated method or the foot-to-foot method. The electrocardiogram-gated method measures the time lapse between R wave of the electrocardiogram and the foot of the carotid artery waveform, and subtracts this value from the time lapse of the R wave and the foot of the femoral artery waveform. The foot-to-foot method uses tonometry or oscillometry to simultaneously measure the carotid and femoral artery waveforms; the lapsed time between the 'feet' of these waveforms serves as the denominator of the pulse wave velocity equation.

antegrade and retrograde waves. The antegrade (P1) and retrograde (P2) waves create two pressure peaks in systole. The difference in magnitude between these peaks is defined as the augmentation pressure. The augmentation index is the augmentation pressure divided by the pulse pressure (systolic blood pressure minus diastolic blood pressure) and is expressed as % (Fig 4). Higher augmentation index values are associated with increased cardiovascular risk.[26]

How is augmentation index measured?

Using the pulse wave velocity analyser that is used to measure pulse wave velocity, the central arterial pulse pressure waveform is obtained. This composite waveform contains both the antegrade wave and the retrograde wave. Augmentation pressure is then calculated as follows:

Augmentation index (%) = (P2 – P1) ÷ Pulse pressure

Pulse pressure = Systolic blood pressure – Diastolic blood pressure

Limitations/quality control

Table 1 lists the ideal conditions for measurement of pulse wave velocity and augmentation index.

Owing to ethical reasons, pulse wave velocity and augmentation index have not been validated in children by simultaneous intra-arterial stiffness measurements using catheters and pressure manometers.[16] Data regarding reproducibility of these techniques in children are also limited. Available reference values in children are from studies with small sample sizes and do not take into consideration any racial differences that may exist in arterial stiffness.[16] Correlation of pulse wave velocity and augmentation index measurements with future cardiovascular disease or mortality is not available as such long-term studies have not yet been conducted.

Placing a femoral probe often requires the patient to undress, which can be uncomfortable for some children. Thus, oscillometric technique may have an advantage over tonometry as direct palpation of the artery is not required. Pulse travel distance must be measured accurately, as a small error in measurement can influence the absolute value of pulse wave velocity.[22,27] Direct measurement of the distance between the pulse points can also be challenging; hence, different methods are used to estimate the pulse wave travel distance. These methods for measuring distance are approximations of the true distance travelled by the pulse wave; therefore, comparing pulse wave velocity data between laboratories can be difficult unless distance measurements are accurate and specified.[22,28] Measuring the pulse travel distance in obese children is difficult and can lead to its overestimation leading to falsely elevated pulse wave velocity.[28] Children add another layer of complexity owing to the shorter pulse travel distance, which can amplify any error in measurement.

Reference values for pulse wave velocity and augmentation index in children

Available reference values for pulse wave velocity and augmentation index for healthy children are presented in Figures 5 and 6, respectively. The pulse

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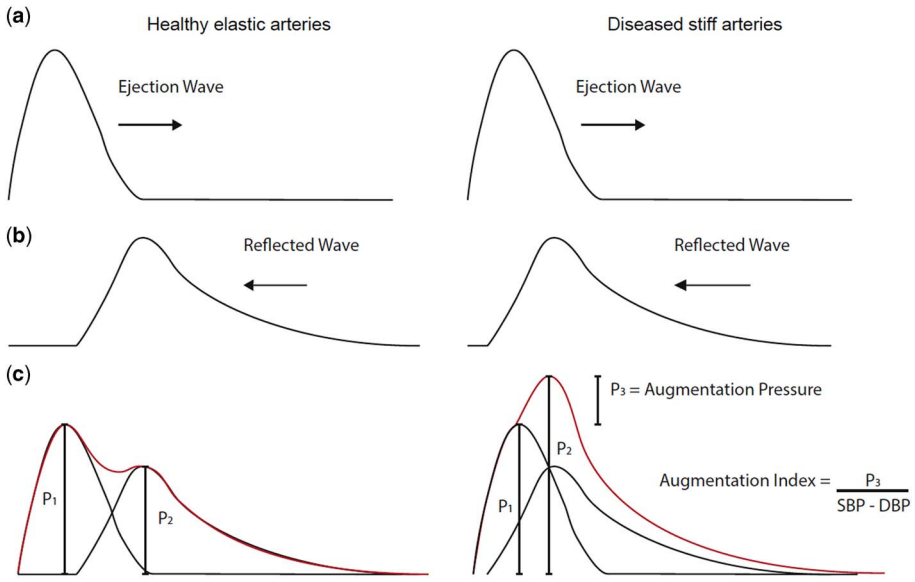

Figure 4.
Augmentation index.
A- The ejection wave travels forward through the artery.
B- Due to resistance at branch points on the artery, the reflected wave is transmitted in a retrograde fashion.
C- The ejection wave (P1) and reflected wave (P2) combine to form a waveform. In elastic arteries (left panel), the reflected wave returns later than with stiffer arteries (right panel), where reflected wave returns earlier and 'augments' the ejection wave. The difference between the ejection wave and the reflected wave is augmentation pressure (P3). The augmentation index is augmentation pressure divided by the pulse pressure.

Table 1. Ideal conditions for measurement of pulse wave velocity and augmentation index.

Patient considerations
Child should be resting in supine position
Room should be controlled for temperature (21°C)
Vasoactive drugs should be avoided 12–24 hours preceding measurement
Meals should be avoided 2.5–4 hours before measurement
Smoking and caffeinated beverages should be avoided 4 hours before the study
Talking should be minimised during measurement
Examination room should be low stimulus and noise free
Young children may watch a movie to minimise anxiety
Familiarise the child with the testing to decrease anxiety
Technical considerations
Take two consecutive pulse wave velocity and augmentation index measurements over 10–15 minutes
Measure pulse travel distance in triplicate

wave velocity reference values are based on age in years or height in centimetres {Reusz et al (n = 1008, 49% males)[29]}, whereas the augmentation index reference values are based on age in years {Hidvegi et al (n = 4619, 54% males)[30]}. In general, increasing age, height, weight, and blood pressure are associated with increased pulse wave velocity.[29,31,32,33] Pulse wave velocity is relatively constant in the very young (3–8-year-olds), but increases thereafter.[32] Gender differences in pulse wave velocity tend to be minimal, and can generally be explained by discrepancies in height. As males outgrow females during adolescence, their pulse wave velocity increases comparatively.[29] In contrast, augmentation index decreases gradually with increasing age in both boys and girls. This is likely owing to the shorter aortic length resulting in early return of the reflected wave in younger children. Augmentation index plateaus around the age of 12 years in girls and age of 15 years in boys. Augmentation index is higher in females indicative of the gender-specific aortic wall characteristics after puberty.[30]

Part II

In this section, we will review pertinent studies that used pulse wave velocity or augmentation index to assess arterial health in commonly occurring conditions in children. Table 2 summarises the findings of pulse wave velocity and augmentation index measurements in various conditions in children.

Obesity

Childhood obesity results in several morbidities that affect the cardiovascular system prematurely. In adults, obesity, specifically central adiposity, is associated with increased pulse wave velocity[34,35] and

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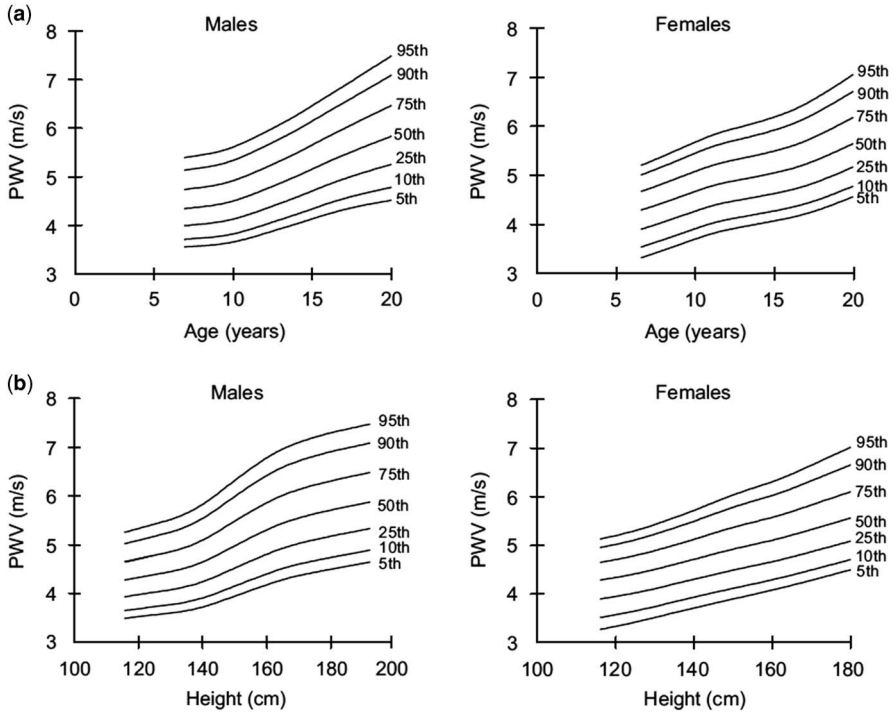

Figure 5.
Pulse wave velocity percentile curves according to age (a) and height (b). Adapted from Reusz et al[29].

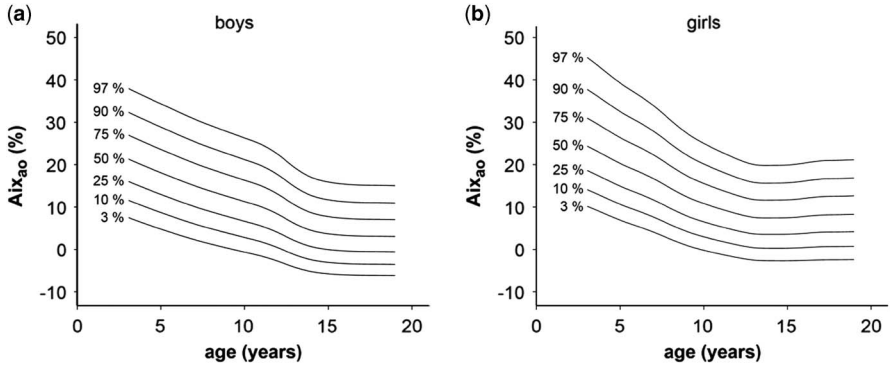

Figure 6.
Augmentation index percentile curves based on age in boys (a) and girls (b). Adapted from Hidvegi et al[30].

weight loss is reported to decrease central pulse wave velocity.[36]

Obesity is associated with functional adaptations such as increased arterial diameter[37] and volume overload, resulting in decreased total peripheral resistance. Some cross-sectional studies show either no association or an inverse relationship between obesity and pulse wave velocity in children.[38,39,40] A study of 501 children and adolescents aged 8–18 years assessed the impact of obesity and blood pressure on pulse wave velocity. The subjects were divided based on blood pressure into normotensive, borderline hypertensive, and hypertensive groups, and based on body weight into normal, overweight, and obese groups. There was a graded increase in pulse wave velocity with increasing blood pressure, but there was an inverse relationship between central pulse wave velocity and body mass index z score. In fact, obesity was noted to blunt the expected increment in pulse wave velocity of hypertensive and borderline hypertensive subjects.[40] In another large longitudinal birth cohort study, investigators performed a cross-sectional examination in 6576 children aged 10–11 years and found elevated heart rate and blood pressure in overweight children, but there was an inverse relationship with peripheral pulse wave

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Table 2. Summary of pulse wave velocity and augmentation index measurements in various conditions in children.

Conditions	Pulse wave velocity	Augmentation index
Obesity	↓↑	↑
Systemic hypertension	↑	↔↑
Insulin resistance	↑↔	↑ ↔
Type 2 diabetes mellitus	↑	↑
Type 1 diabetes mellitus	↑ ↔	↑
Dyslipidaemia	↑ ↔	↑
Physical inactivity	↑ ↔	↑ ↔
Chronic kidney disease	↑ ↔	↑
Post-renal transplant	↑↓ ↔	↑ ↔
Coarctation of aorta	↑	Insufficient data
Tetralogy of Fallot	↑	↑
Fontan	↑	Insufficient data
Prematurity	↔	↑ ↔
Small for gestational age	↑	Insufficient data
Kawasaki disease	↑	Insufficient data

↑ = increased; ↓ = decreased; ↔ = no change

velocity.[39] This is the largest reported study linking body weight and pulse wave velocity in pre-pubertal children. A small case–control study of 33 obese children and adolescents (13.9 ± 1.6 years) and 18 lean controls (14.3 ± 2.2 years) showed that peripheral pulse wave velocity was lower in obese than in lean controls (6.2 ± 0.8 versus 7.0 ± 0.9 m/second, respectively).[38] These inverse relationships between obesity and pulse wave velocity perhaps reflect physiologic adaptations (i.e. larger arteries) in the short term. Thus, there is likely a window of opportunity in early childhood to target and potentially reverse obesity before adverse vascular changes manifest.[39]

At some point, these functional adaptations can no longer compensate for the increased arterial pressures associated with obesity. The tension on the arterial wall eventually causes the wall to stiffen.[37] This phenomenon is supported by other cross-sectional studies in children that show increased pulse wave velocity in obesity.[41–43] A study of 670 youth aged 10–24 years recruited patients with type 2 diabetes mellitus and matched them to obese and lean controls. There was a stepwise increase in central pulse wave velocity and augmentation index from lean to obese to type 2 diabetics, but there were no significant differences in peripheral pulse wave velocity among the groups.[43] The study was limited by its cross-sectional nature, thus making it difficult to determine the time course of involvement of various arterial sites. "Lifestyle of Our Kids" is an Australian prospective cohort study designed to investigate the effect of physical activity on health and development. Investigators performed cross-sectional measurements of pulse wave velocity and compared it with body composition and a 7-day pedometer count in 573 children (10.1 ± 0.3 years). They found a positive correlation between central pulse wave velocity and body mass index, waist circumference, and adiposity, and a negative correlation with pedometer count.[42] In another study of 193 children aged 13.2 ± 0.7 years, central adiposity was associated with increased central pulse wave velocity.[44]

There are some longitudinal data linking obesity to increased arterial stiffness in children as well. In a Swedish study of 28 obese children aged 10.2–17.6 years (mean age 13.8 years) and 14 lean children aged 11.5–16.1 years (mean age 13.8 years), longitudinal measurements of pulse wave velocity were made over a period of 5 years. There was a 25% increase in peripheral pulse wave velocity in obese children compared with a 3% increase in age- and gender-matched lean controls during the study period.[41] The Cardiovascular Risk in Young Finns Study recruited 1691 adults[45] aged 30–45 years with known risk factor data since childhood. A favourable change in obesity status from childhood to adulthood was associated with a lower pulse wave velocity in adulthood.

These studies support the notion that while pulse wave velocity may not be increased at the outset in childhood obesity, obesity does aggravate arterial stiffening over time. All these findings also support early intervention in obesity – when the vascular changes may still be reversible.[41,45]

Hypertension

Hypertension is a well-recognised cardiovascular risk factor and in adults pulse wave velocity evaluation is recommended in clinic settings for assessment of subclinical target organ damage.[46] Childhood hypertension also causes early cardiovascular damage as evident by increased carotid artery intima–media thickness and left ventricular mass index.[47] Studies in children have found a direct association between blood pressure (both systolic and diastolic) and pulse wave velocity.[32,40,48,49,50–52] Some studies have found an association between pre-hypertension in children and increasing pulse wave velocity as well[40,50,52], indicating that vascular changes may occur even with subtle elevations in blood pressure. A study of 501 children and adolescents aged 8–18 years assessed the impact of blood pressure on pulse wave velocity and augmentation index. The investigators divided the subjects based on blood pressure into normotensive, borderline hypertensive, and hypertensive groups. There was a graded increase in pulse wave velocity with increasing blood pressure

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without any significant changes noted in augmentation index.[40] Another study of 970 Japanese children (52% boys) found similar increases in peripheral pulse wave velocity with increases in heart rate and blood pressure.[48] A study of 723 youth aged 10–23 years (29% with type 2 diabetes mellitus) divided patients by blood pressure level into normotensive, pre-hypertensive, and hypertensive groups. The investigators found a graded increase in pulse wave velocity, augmentation index, and left ventricular mass index as blood pressure increased.[52]

The effect of blood pressure on pulse wave velocity is thought to be multifactorial: increases in blood pressure results in a functional increase in pulse wave velocity (at higher afterload, the heart has to pump out blood at a higher velocity), and chronic high blood pressure causes structural changes in the arterial wall owing to shear stress, and stiffens arteries. Children of parents with hypertension have increased pulse wave velocity compared with children of normotensive parents independent of the child's blood pressure status, indicating perhaps a blood pressure-independent, genetic component as well.[53] In view of these data, further studies are needed utilising pulse wave velocity and augmentation index measures to determine the optimal management of hypertension in children.

Insulin resistance

Insulin resistance is associated with increased pulse wave velocity in adults.[54,55] Studies in children, however, have shown mixed results. In a study of 93 children, aged 10 ± 0.1 years, insulin resistance was not associated with central pulse wave velocity.[56] A study of 343 adolescents and young adults aged 15–28 years old showed an association between insulin resistance, central pulse wave velocity, and augmentation index. However, after adjusting for other cardiovascular risk factors such as age, sex, body mass index, and blood pressure, insulin resistance was no longer an independent predictor of central pulse wave velocity. Some limitations of this study were its cross-sectional design and a selection bias with exclusion of lean insulin-resistant individuals.[57] In another study including 241 obese youth, neither central pulse wave velocity nor augmentation index were increased in obese youth with glucose intolerance (18.0 ± 3.6 years) compared with those with normal glucose tolerance (18.3 ± 3.0 years). However, their brachial artery distensibility was decreased, indicating peripheral vascular dysfunction. This may suggest non-uniform progression of atherosclerosis, with peripheral arteries likely being affected earlier in the pre-diabetic state than central arteries.[58] In contrast, in an Australian study conducted on a population-based birth cohort of 147 twin pairs (7–11 years), insulin resistance was associated with increased central pulse wave velocity.[59]

Thus, insulin resistance may play a role in modulating arterial stiffness, but other cardiovascular risk factors may be more important determinants of vascular health in these children.

Type 2 diabetes mellitus

In adults with type 2 diabetes mellitus, central pulse wave velocity is increased compared with controls.[60] In a study of 670 youth aged 18.1 ± 3.3 years, obese youth with type 2 diabetes mellitus had increased central and peripheral pulse wave velocity and augmentation index compared with those obese and without type 2 diabetes mellitus or lean controls. Multivariate analysis revealed type 2 diabetes mellitus to be an independent predictor of central pulse wave velocity.[43]

In summary, arterial stiffness is increased in children with type 2 diabetes mellitus especially if associated with obesity.

Type 1 diabetes mellitus

In adults with type 1 diabetes mellitus, central pulse wave velocity is increased even in the absence of cardiovascular disease.[61] Paediatric studies have found a similar association between Type 1 diabetes mellitus and pulse wave velocity.[62–65] A study of 30 children with type 1 diabetes mellitus found no difference in central pulse wave velocity when compared with controls, but found a significant increase in augmentation index, a combined measure of peripheral and central stiffness.[66] SEARCH for Diabetes in Youth Study is a multicentre study aimed at understanding more about diabetes among children and young adults in the United States. Investigators recruited 535 youth with type 1 diabetes mellitus (14.6 ± 3.3 years) and compared their pulse wave velocity, augmentation index, and brachial distensibility with 241 healthy controls. The average duration of diabetes was 68.4 ± 8.3 months. About 10% of the type 1 diabetics had increased central pulse wave velocity and augmentation index, whereas 33% had decreased brachial artery distensibility – a measure of peripheral arterial stiffness.[64] The authors concluded that arterial stiffness is increased in children with type 1 diabetes mellitus, with peripheral arteries likely affected more than the central arteries. Another subset of patients from the SEARCH for Diabetes in Youth study included youth (10–23-year-olds) with type 1 diabetes mellitus ($n = 535$) and type 2 diabetes Mellitus ($n = 60$). Youth with type 2 diabetes mellitus had higher

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central pulse wave velocity and augmentation index than youth with type 1 diabetes mellitus.[65] Pulse wave velocity was associated with central adiposity and blood pressure, independent of diabetes type. The authors concluded that worse arterial stiffness in type 2 diabetes mellitus may be related to its insidious onset that allows the arteries to stiffen before disease recognition and interventions[65] and clustering of cardiovascular risk factors such as obesity and hypertension that can evolve to type 2 diabetes mellitus. Some limitations of this study include limited number with type 2 diabetes mellitus, exclusion of healthy controls, and its cross-sectional design.

Further studies are needed to identify key modifiable risk factors that are associated with cardiovascular involvement in type 1 and type 2 diabetes mellitus and role of interventions including optimal glucose control in mitigating cardiovascular risk in such children.

Dyslipidaemia

Dyslipidaemia, specifically elevated low-density lipoprotein cholesterol, is associated with premature cardiovascular disease.[3] High-density lipoprotein cholesterol is known for its anti-atherosclerotic properties.[67] Apolipoprotein-B, also known for its atherosclerotic properties, is regarded as another important risk factor for ischaemic heart disease in adults.[68] In a study of 267 adolescents aged 15.4 ± 2.2 years, pulse wave velocity was significantly elevated in those with high low-density lipoprotein cholesterol. In those with borderline low-density lipoprotein cholesterol levels, subjects with high apolipoprotein-B had increased pulse wave velocity as compared with those with normal apolipoprotein-B levels.[69] However, in another study looking at 30 children (mean age 12 ± 2 years) with familial hypercholesterolaemia (low-density lipoprotein cholesterol 213 ± 52 mg/dL) and 30 controls (low-density lipoprotein cholesterol 89 ± 18 mg/dL), there was no difference in central pulse wave velocity between groups.[70] The SEARCH for Diabetes in Youth Study examined 535 youth with type 1 diabetes mellitus (mean age 14.6 ± 3.3 years) and 241 healthy controls (mean age 17.8 ± 3.5 years), and found that those with high low-density lipoprotein cholesterol had increased augmentation index.[64] In another large cross-sectional study of 893 youth (10–26 year-olds), laboratory, anthropometric, blood pressure, and arterial stiffness data were collected. Subjects were stratified into tertiles of triglyceride to high-density lipoprotein cholesterol ratio. There was a progressive increase in central pulse wave velocity and augmentation index as the triglyceride to high-density lipoprotein cholesterol ratio (a measure of small, dense low-density lipoprotein cholesterol) increased.[71]

Thus, dyslipidaemia may be associated with arterial stiffness, and measuring pulse wave velocity and augmentation index measures in such youth may be helpful in identifying those requiring aggressive interventions. Further studies are needed to determine the optimal timing for pharmacological intervention and key lipid markers to follow in children with dyslipidaemia and how that may influence arterial health.

Physical inactivity

In adults, aerobic exercise decreases pulse wave velocity[72], whereas combined aerobic and resistance training may have reduced beneficial effects.[73] Studies in children have examined the roles of different types and intensities of training or physical inactivity on pulse wave velocity and augmentation index using gadgets such as pedometers or accelerometers that objectively measure physical activity.[42,44,43] One study showed an inverse relationship between the 7-day pedometer count and pulse wave velocity.[42] Two studies showed an inverse relationship between physical activity and augmentation index, but not pulse wave velocity.[44,43]

Other studies in children have used self-reported physical activity and/or physical activity questionnaires. A Canadian study recruited 485 youth aged ~12.5 years from the 1995 Manitoba birth cohort. The investigators used a 12-month recall instrument to assess physical activity and found no association between physical activity and peripheral pulse wave velocity or augmentation index.[74] A study from India of 250 youth aged 6–17 years (mean age 11.4 years) used a one-time activity questionnaire and found moderate physical activity to be inversely associated with pulse wave velocity.[75] In another report, in 10-year-olds, pulse wave velocity was inversely associated with a 24-hour self-reported physical activity.[56] In a longitudinal Swedish study, pulse wave velocity in 241 children and adolescents (mean age 10 years at study entry) was assessed and repeat measurements were obtained in 162 of them 3 years later. Peripheral pulse wave velocity was increased in both males and females, but greater in males with decreased self-reported physical activity.[76]

In summary, most studies show that increased aerobic physical activity has beneficial effects on arterial stiffness in children, although it is not entirely clear whether pulse wave velocity or augmentation index is more sensitive to measure these beneficial effects. Further studies should evaluate whether strategies to promote physical activity

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and reduce sedentary time in children optimise their arterial health and decrease premature cardiovascular disease.

Chronic kidney disease and renal transplantation

With advances in renal replacement therapy, premature cardiovascular disease is the leading cause of death in end-stage renal disease.[77] Pulse wave velocity and augmentation index are strong predictors of mortality in adults with end-stage renal disease.[21] In children with end-stage renal disease receiving dialysis, central pulse wave velocity,[78–80] peripheral pulse wave velocity[81], and augmentation index[78] were all increased. One study found a stepwise increase in central pulse wave velocity between 18 healthy controls, 33 children with end-stage renal disease not yet requiring dialysis, and 37 children with end-stage renal disease on dialysis.[80] Another study looking at 24 children with chronic kidney disease not requiring dialysis did not show any difference in central pulse wave velocity in these children when compared with 48 age-matched healthy controls.[82] Thus, while the more severe chronic kidney disease and end-stage renal disease requiring dialysis cause arterial stiffening, the arterial changes in less advanced stages of chronic kidney disease may not be significant.[82] Thus, early identification and intervention may preserve arterial health in children with chronic kidney disease.

A study looking at 85 children (5–18-year-olds) with end-stage renal disease on dialysis for ⩾6 months showed that peripheral pulse wave velocity was increased in these children compared with controls, and pulse wave velocity correlated with serum parathyroid hormone, phosphorus, and the calcium phosphate product. This suggests that a procalcific state may cause tunica–media calcification leading to arteriosclerosis – a process distinct from atherosclerosis – and this may play a role in increasing arterial stiffness as well.[81] In another study examining uraemic children, CD144+ endothelial microparticle, which is a marker of endothelial dysfunction, and mean blood pressure were independently related to central pulse wave velocity.[80] Skin auto-fluorescence – a marker of advanced glycation end products – positively correlated with central pulse wave velocity in children with chronic kidney disease.[83] These studies suggest that metabolic dysfunction and pro-inflammatory states in uraemia may play a predominant role in causing arterial stiffening.

Studies in adults show that renal transplantation decreases the risk of cardiovascular complications, although the risk still remains three to five times higher than the general population.[84] Although renal transplantation improves uraemia, transplantation-associated immune suppression may also have consequences on the vasculature. To address the question of whether renal transplantation can ameliorate arterial stiffness in end-stage renal disease children, central pulse wave velocity and augmentation index were measured 6 months before and 6 months after renal transplantation in 15 children aged 11.1 ± 4.8 years who were on dialysis for 12.9 ± 7.4 months before transplantation. There was no significant difference in either measure after transplantation; however, there was an inverse relation between central pulse wave velocity and graft function in this prospective study.[85] A major limitation of this study was its small sample size and a follow-up time period of only 6 months, which may be too short to evaluate vascular changes. Another study compared 25 children following renal transplant with 11 children with end-stage renal disease and found that only when a post-transplantation creatinine clearance of >90 ml/minute/1.73 m^2 was achieved there was improvement in the central pulse wave velocity.[86] Another study showed that central pulse wave velocity and augmentation index were higher in 36 children who had received renal transplantation compared with 49 age-matched healthy controls.[87] A study of 41 children examining whether weight gain following renal transplantation, likely due to corticosteroid use, is related to increased pulse wave velocity found no difference in central pulse wave velocity between lean and overweight groups.[88]

These studies together indicate that end-stage renal disease leads to arterial stiffening, which can partially be ameliorated by renal transplantation. Improvements may not be detected in the short term following renal transplantation, but better renal function may improve arterial health.

CHD

A variety of palliated or repaired congenital heart defects are associated with alterations in the vasculature.

Coarctation of the aorta

Despite anatomically successful repair of coarctation of the aorta, these patients are at an increased risk of developing hypertension and premature cardiovascular disease.[89,90] Hypertensive adolescents (n = 9) with repaired coarctation of the aorta had increased pulse wave velocity compared with 20 age-matched controls.[91] This study excluded patients having any residual aortic narrowing. In another study of 40 normotensive children with anatomically successful repair of coarctation of the aorta (mean age 12 ± 8 years), pulse wave velocity was increased

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compared with 20 age- and sex-matched controls. This study used magnetic resonance imaging to assess pulse wave velocity and excluded those with hypertension at rest and residual arch obstruction. This indicates that residual pathophysiologic abnormalities exist in the aorta even in the absence of hypertension or anatomic obstruction.[92]

These findings emphasise the importance of continued follow-up, and further studies are needed to determine optimal medical and lifestyle management, especially in the absence of hypertension or anatomic obstruction.

Tetralogy of Fallot

In children with tetralogy of Fallot, the anatomic abnormalities also extend to the aorta with aortic root dilatation noted often. Histologic studies have shown arterial wall abnormalities such as medial necrosis, fibrosis, and elastic fibre fragmentation.[93,94] In adults who had surgical repair of tetralogy of Fallot during childhood, the aortic root is known to progressively dilate[95,96]; this can be associated with aortic valve regurgitation and aortic dissection.[97]

A study measured pulse wave velocity during cardiac catheterisation in 37 infants and children before corrective surgery for tetralogy of Fallot and compared it with 55 controls who had ventricular septal defect or patent ductus arteriosus. Pulse wave velocity was significantly elevated in uncorrected tetralogy of Fallot, even after controlling for age, sex, and haemodynamic burden on the aortic wall.[98] In a study of 161 children, the proximal aorta had increased pulse wave velocity in repaired and unrepaired tetralogy of Fallot compared with controls. Pulse wave velocity in distal aorta was similar in the repaired tetralogy of Fallot, unrepaired tetralogy of Fallot, and control groups. This suggests an intrinsic defect of the proximal aorta in children with tetralogy of Fallot that is present de novo and persists after surgical repair.[99] In a case–control study in 31 youth with surgically repaired tetralogy of Fallot, both central pulse wave velocity and augmentation index were increased and correlated with the aortic root size; there was no concomitant increase in peripheral pulse wave velocity, suggesting only central arterial stiffening.[100] Similarly, in another study of 38 children with corrected tetralogy of Fallot (mean age 6.3 ± 4.1 years) and 55 controls, the tetralogy of Fallot group showed significant association between pulse wave velocity and aortic root diameter.[101] Interestingly, pulse wave velocity at baseline in 32 children predicted increased aortic diameter at follow-up 7.6 ± 2.0 years later, indicating that pulse wave velocity may be used as a marker for predicting aortopathy.[102]

In summary, proximal aortic arterial stiffness is noted in patients with tetralogy of Fallot. Further studies are needed to see whether interventions aimed at reducing arterial stiffness could reduce the rate of aortic root dilatation in this population.

Fontan

Children before completion of the Fontan procedure (mean age 28 ± 25 months) had similar central pulse wave velocity as children with other congenital heart disease with two-ventricle physiology (mean age 35 ± 24 months).[103] In 28 post-Fontan youth (mean age 14.8 ± 1.3 years) and 54 age-matched controls, peripheral but not central pulse wave velocity was increased in Fontan youth compared with controls.[104] In another study of 22 Fontan youth (mean age 14.9 years) and 31 controls (mean age 15.2 years), central pulse wave velocity was increased in Fontan youth compared with controls.[105]

Thus, abnormal arterial stiffness may develop in teenage Fontan patients, although mechanisms and progression remain unclear. Future studies are needed to see whether strategies aimed at improving arterial stiffness by improving physical activity and fitness could delay the progression of ventricular dysfunction and improve the quality of life in this population.

Prematurity and small for gestational age

Preterm birth and being small for gestational age have been associated with hypertension[106,107], premature coronary artery disease[108], and increased cardiovascular mortality[109] in adulthood.

In a study of 68 children (age 11 years) who were born extremely premature (gestational age 24.9 weeks), augmentation index was increased when compared with 90 age- and sex-matched controls born at term, but central pulse wave velocity and blood pressures were not different between groups, suggesting preferential involvement of the peripheral muscular arteries in the extremely premature group.[110] In a study looking at 34 girls born preterm ($\leqslant$34 weeks gestation) and 32 age- and sex-matched controls who were born term and appropriate weight for gestation, no between-group differences were found in either peripheral pulse wave velocity or augmentation index when tested at 16.5 years of age. However, resting peripheral skin blood flow, used to measure underlying resistance vessel smooth muscle tone, was reduced in preterm females, indicating increased peripheral vascular resistance.[111] In 39 children who were small for gestational age (mean age 10.5 ± 1.4 years) and 41 age- and sex-matched controls, central pulse wave velocity was increased in the small for gestational age group compared with controls despite no difference in blood pressures.[112]

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A cross-sectional study of 86 children aged 8.2 ±1.7 years divided children into three groups: children who were both preterm and small for gestational age (n = 15), children who were born preterm but appropriate weight for gestational age (n = 36), and those born at term with appropriate weight for gestational age (n = 35). Those preterm and small for gestational age had the highest peripheral pulse wave velocity, whereas children born preterm and term with appropriate weight for age had similar pulse wave velocities.[113]

In summary, being both preterm and particularly small for gestational age is detrimental to arterial health. Extreme prematurity and small for gestational age are associated with adverse vasculature emphasising the need for continued, long-term cardiovascular surveillance of this population.

Kawasaki disease

Kawasaki disease is a common acquired cardiovascular disease in children and affects medium-sized muscular arteries. Several studies show increased peripheral pulse wave velocity[114–116] in subjects with a history of Kawasaki disease when compared with controls; elevation in pulse wave velocity was, however, independent of coronary artery involvement[114–117], indicating that all children with history of Kawasaki disease may be at an increased risk of vascular complications. Encouragingly, in one study there was a significant decrease in pulse wave velocity in 11 patients (age 7–25 years) with Kawasaki disease following treatment with statins for 12 months.[118]

Conclusion

Risk factors such as obesity, hypertension, insulin resistance, dyslipidaemia, and physical inactivity often cluster in children who are otherwise healthy or have underlying CHD or acquired heart diseases, leading to accelerated atherosclerosis. Pulse wave velocity and augmentation index are easy-to-use non-invasive tools that measure arterial stiffness – a measure of arterial function and structure – and can quantify the effects of such risk factors on the vasculature. In this article, we have reviewed the physics and techniques for measurement of pulse wave velocity and augmentation index and summarised current knowledge of these measurements in children with prevailing chronic conditions. At this time, there are not enough data to suggest that these tools should be used as routine, clinical testing modalities in children. Methodological consistencies are crucial as heterogeneity in methods can greatly influence the measurements. Although some published reference values for pulse wave velocity and augmentation index exist in children, larger studies are needed comparing these measurements in various populations including different races.

Studies narrated in this review have shown that pulse wave velocity and augmentation index (arterial stiffness measures) are deranged in various, commonly prevailing medical conditions in children and adolescents. Adult data linking arterial stiffness to cardiovascular events and mortality are causes for concern, and suggest that these vascular measures when deranged are likely to be detrimental to the child's long-term cardiovascular health. Thus, even though longitudinal data correlating deranged arterial health in childhood with cardiovascular mortality are lacking at this time, one could consider selectively using these testing modalities to risk-stratify children and target the ones with the highest risk for the most aggressive interventions. Further studies are needed to assess whether such interventions can improve arterial health in children and whether this indeed optimises long-term cardiovascular health.

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Conflicts of Interest

None.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Executive summary: heart disease and stroke statistics – 2010 update: a report from the American Heart Association. Circulation 2010; 121: 948–954.
2. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol 2005; 25: 932–943.
3. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011; 128 (Suppl 5): S213–S256.
4. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992; 340: 1111–1115.
5. Crouse JR 3rd, Craven TE, Hagaman AP, et al. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation 1995; 92: 1141–1147.
6. Riley WA, Barnes RW, Evans GW, et al. Ultrasonic measurement of the elastic modulus of the common carotid artery. The Atherosclerosis Risk in Communities (ARIC) Study. Stroke 1992; 23: 952–956.
7. Kelly AS, Wetzsteon RJ, Kaiser DR, et al. Inflammation, insulin, and endothelial function in overweight children and adolescents: the role of exercise. J Pediatr 2004; 145: 731–736.

8. Aggoun Y, Farpour-Lambert NJ, Marchand LM, et al. Impaired endothelial and smooth muscle functions and arterial stiffness appear before puberty in obese children and are associated with elevated ambulatory blood pressure. Eur Heart J 2008; 29: 792–799.
9. Jarvisalo MJ, Raitakari M, Toikka JO, et al. Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. Circulation 2004; 109: 1750–1755.
10. de Jongh S, Lilien MR, op't Roodt J, et al. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. J Am Coll Cardiol 2002; 40: 2117–2121.
11. Kari JA, Donald AE, Vallance DT, et al. Physiology and biochemistry of endothelial function in children with chronic renal failure. Kidney Int 1997; 52: 468–472.
12. Meyer AA, Kundt G, Steiner M, et al. Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. Pediatrics 2006; 117: 1560–1567.
13. Woo KS, Chook P, Yu CW, et al. Effects of diet and exercise on obesity-related vascular dysfunction in children. Circulation 2004; 109: 1981–1986.
14. Freedman DS, Dietz WH, Tang R, et al. The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. Int J Obes Relat Metab Disord 2004; 28: 159–166.
15. Stoner L, Young JM, Fryer S. Assessments of arterial stiffness and endothelial function using pulse wave analysis. Int J Vasc Med 2012; 2012: 903107.
16. Urbina EM, Williams RV, Alpert BS, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension 2009; 54: 919–950.
17. Blacher J, Asmar R, Djane S, et al. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999; 33: 1111–1117.
18. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55: 1318–1327.
19. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 2010; 121: 505–511.
20. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37: 1236–1241.
21. London GM, Blacher J, Pannier B, et al. Arterial wave reflections and survival in end-stage renal failure. Hypertension 2001; 38: 434–438.
22. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588–2605.
23. Hickson SS, Butlin M, Broad J, et al. Validity and repeatability of the Vicorder apparatus: a comparison with the SphygmoCor device. Hypertens Res 2009; 32: 1079–1085.
24. Grotenhuis HB, Westenberg JJ, Steendijk P, et al. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. J Magn Reson Imaging 2009; 30: 521–526.
25. Calabia J, Torguet P, Garcia M, et al. Doppler ultrasound in the measurement of pulse wave velocity: agreement with the Complior method. Cardiovasc Ultrasound 2011; 9: 13.
26. Nurnberger J, Keflioglu-Scheiber A, Opazo Saez AM, et al. Augmentation index is associated with cardiovascular risk. J Hypertens 2002; 20: 2407–2414.
27. Chirinos JA. Arterial stiffness: basic concepts and measurement techniques. J Cardiovasc Transl Res 2012; 5: 243–255.
28. Van Bortel LM, Duprez D, Starmans-Kool MJ, et al. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. Am J Hypertens 2002; 15: 445–452.
29. Reusz GS, Cseprekal O, Temmar M, et al. Reference values of pulse wave velocity in healthy children and teenagers. Hypertension 2010; 56: 217–224.
30. Hidvegi EV, Illyes M, Molnar FT, et al. Influence of body height on aortic systolic pressure augmentation and wave reflection in childhood. J Human Hypertens 2015; 29: 495–501.
31. Fischer DC, Schreiver C, Heimhalt M, et al. Pediatric reference values of carotid-femoral pulse wave velocity determined with an oscillometric device. J Hypertens 2012; 30: 2159–2167.
32. Hidvegi EV, Illyes M, Benczur B, et al. Reference values of aortic pulse wave velocity in a large healthy population aged between 3 and 18 years. J Hypertens 2012; 30: 2314–2321.
33. Elmenhorst J, Hulpke-Wette M, Barta C, et al. Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. Atherosclerosis 2015; 238: 9–16.
34. Recio-Rodriguez JI, Gomez-Marcos MA, Patino-Alonso MC, et al. Abdominal obesity vs general obesity for identifying arterial stiffness, subclinical atherosclerosis and wave reflection in healthy, diabetics and hypertensive. BMC Cardiovasc Disord 2012; 12: 3.
35. Scuteri A, Orru M, Morrell CH, et al. Associations of large artery structure and function with adiposity: effects of age, gender, and hypertension. The SardiNIA Study. Atherosclerosis 2012; 221: 189–197.
36. Dengo AL, Dennis EA, Orr JS, et al. Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. Hypertension 2010; 55: 855–861.
37. Cote AT, Harris KC, Panagiotopoulos C, et al. Childhood obesity and cardiovascular dysfunction. J Am Coll Cardiol 2013; 62: 1309–1319.
38. Dangardt F, Osika W, Volkmann R, et al. Obese children show increased intimal wall thickness and decreased pulse wave velocity. Clin Physiol Funct Imaging 2008; 28: 287–293.
39. Charakida M, Jones A, Falaschetti E, et al. Childhood obesity and vascular phenotypes: a population study. J Am Coll Cardiol 2012; 60: 2643–2650.
40. Lurbe E, Torro I, Garcia-Vicent C, et al. Blood pressure and obesity exert independent influences on pulse wave velocity in youth. Hypertension 2012; 60: 550–555.
41. Dangardt F, Chen Y, Berggren K, et al. Increased rate of arterial stiffening with obesity in adolescents: a five-year follow-up study. PloS one 2013; 8: e57454.
42. Sakuragi S, Abhayaratna K, Gravenmaker KJ, et al. Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. Hypertension 2009; 53: 611–616.
43. Urbina EM, Kimball TR, Khoury PR, et al. Increased arterial stiffness is found in adolescents with obesity or obesity-related type 2 diabetes mellitus. J Hypertens 2010; 28: 1692–1698.
44. Arnberg K, Larnkjaer A, Michaelsen KF, et al. Central adiposity and protein intake are associated with arterial stiffness in overweight children. J Nutr 2012; 142: 878–885.
45. Aatola H, Hutri-Kahonen N, Juonala M, et al. Lifetime risk factors and arterial pulse wave velocity in adulthood: the cardiovascular risk in young Finns study. Hypertension 2010; 55: 806–811.
46. Mansia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 2007; 16: 135–232.
47. Liang Y, Hou D, Shan X, et al. Cardiovascular remodeling relates to elevated childhood blood pressure: Beijing Blood Pressure Cohort Study. Int J Cardiol 2014; 177: 836–839.
48. Niboshi A, Hamaoka K, Sakata K, et al. Characteristics of brachial-ankle pulse wave velocity in Japanese children. Eur J Pediatr 2006; 165: 625–629.

49. Stergiou GS, Giovas PP, Kollias A, et al. Relationship of home blood pressure with target-organ damage in children and adolescents. Hypertens Res 2011; 34: 640–644.
50. Zhu H, Yan W, Ge D, et al. Cardiovascular characteristics in American youth with prehypertension. Am J Hypertens 2007; 20: 1051–1057.
51. Stergiou GS, Kollias A, Giovas PP, et al. Ambulatory arterial stiffness index, pulse pressure and pulse wave velocity in children and adolescents. Hypertens Res 2010; 33: 1272–1277.
52. Urbina EM, Khoury PR, McCoy C, et al. Cardiac and vascular consequences of pre-hypertension in youth. J Clin Hypertens 2011; 13: 332–342.
53. Kyvelou SM, Vyssoulis GP, Karpanou EA, et al. Arterial stiffness in offspring of hypertensive parents: a pilot study. Int J Cardiol 2008; 129: 438–440.
54. Czernichow S, Bertrais S, Blacher J, et al. Metabolic syndrome in relation to structure and function of large arteries: a predominant effect of blood pressure. A report from the SU.VI.MAX. Vascular Study. Am J Hypertens 2005; 18 (9 Pt 1): 1154–1160.
55. Kasayama S, Saito H, Mukai M, et al. Insulin sensitivity independently influences brachial-ankle pulse-wave velocity in non-diabetic subjects. Diabet Med 2005; 22: 1701–1706.
56. Schack-Nielsen L, Molgaard C, Larsen D, et al. Arterial stiffness in 10-year-old children: current and early determinants. Br J Nutr 2005; 94: 1004–1011.
57. Urbina EM, Gao Z, Khoury PR, et al. Insulin resistance and arterial stiffness in healthy adolescents and young adults. Diabetologia 2012; 55: 625–631.
58. Shah AS, Gao Z, Urbina EM, et al. Prediabetes: the effects on arterial thickness and stiffness in obese youth. J Clin Endocrinol Metab 2014; 99: 1037–1043.
59. McCloskey K, Sun C, Pezic A, et al. The effect of known cardiovascular risk factors on carotid-femoral pulse wave velocity in school-aged children: a population based twin study. J Dev Orig Health Dis 2014; 5: 307–313.
60. Kimoto E, Shoji T, Shinohara K, et al. Preferential stiffening of central over peripheral arteries in type 2 diabetes. Diabetes 2003; 52: 448–452.
61. Llaurado G, Ceperuelo-Mallafre V, Vilardell C, et al. Arterial stiffness is increased in patients with type 1 diabetes without cardiovascular disease: a potential role of low-grade inflammation. Diabetes Care 2012; 35: 1083–1089.
62. Lieberman R, Wadwa RP, Nguyen N, et al. The association between vitamin D and vascular stiffness in adolescents with and without type 1 diabetes. PloS one 2013; 8: e77272.
63. Stakos DA, Schuster DP, Sparks EA, et al. Cardiovascular effects of type 1 diabetes mellitus in children. Angiology 2005; 56: 311–317.
64. Urbina EM, Wadwa RP, Davis C, et al. Prevalence of increased arterial stiffness in children with type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for Diabetes in Youth Study. J Pediatr 2010; 156: 731–737; 37 e1.
65. Wadwa RP, Urbina EM, Anderson AM, et al. Measures of arterial stiffness in youth with type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. Diabetes Care 2010; 33: 881–886.
66. Heilman K, Zilmer M, Zilmer K, et al. Arterial stiffness, carotid artery intima-media thickness and plasma myeloperoxidase level in children with type 1 diabetes. Diabetes Res Clin Pract 2009; 84: 168–173.
67. Rosenson RS, Brewer HB Jr, Chapman MJ, et al. HDL measures, particle heterogeneity, proposed nomenclature, and relation to atherosclerotic cardiovascular events. Clin Chem 2011; 57: 392–410.
68. Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. Circulation 1996; 94: 273–278.
69. Bjornstad P, Nguyen N, Reinick C, et al. Association of apolipoprotein B, LDL-C and vascular stiffness in adolescents with type 1 diabetes. Acta Diabetol 2015; 52: 611–619.
70. Vlahos AP, Naka KK, Bechlioulis A, et al. Endothelial dysfunction, but not structural atherosclerosis, is evident early in children with heterozygous familial hypercholesterolemia. Pediatr Cardiol 2014; 35: 63–70.
71. Urbina EM, Khoury PR, McCoy CE, et al. Triglyceride to HDL-C ratio and increased arterial stiffness in children, adolescents, and young adults. Pediatrics 2013; 131: e1082–e1090.
72. Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation 1993; 88 (4 Pt 1): 1456–1462.
73. Montero D, Vinet A, Roberts CK. Effect of combined aerobic and resistance training versus aerobic training on arterial stiffness. Int J Cardiol 2015; 178: 69–76.
74. Walker DJ, MacIntosh A, Kozyrskyj A, et al. The associations between cardiovascular risk factors, physical activity, and arterial stiffness in youth. J Phys Act Health 2013; 10: 198–204.
75. Pandit DS, Khadilkar AV, Chiplonkar SA, et al. Arterial stiffness in obese children: role of adiposity and physical activity. Indian J Endocrinol Metab 2014; 18: 70–76.
76. Chen Y, Dangardt F, Osika W, et al. Age- and sex-related differences in vascular function and vascular response to mental stress. Longitudinal and cross-sectional studies in a cohort of healthy children and adolescents. Atherosclerosis 2012; 220: 269–274.
77. Groothoff JW, Gruppen MP, Offringa M, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int 2002; 61: 621–629.
78. Covic A, Mardare N, Gusbeth-Tatomir P, et al. Increased arterial stiffness in children on haemodialysis. Nephrol Dial Transplant 2006; 21: 729–735.
79. Kis E, Cseprekal O, Horvath Z, et al. Pulse wave velocity in end-stage renal disease: influence of age and body dimensions. Pediatr Res 2008; 63: 95–98.
80. Dursun I, Poyrazoglu HM, Gunduz Z, et al. The relationship between circulating endothelial microparticles and arterial stiffness and atherosclerosis in children with chronic kidney disease. Nephrol Dial Transplant 2009; 24: 2511–2518.
81. Shroff RC, Donald AE, Hiorns MP, et al. Mineral metabolism and vascular damage in children on dialysis. J Am Soc Nephrol 2007; 18: 2996–3003.
82. Alghamdi M, De Souza AM, White CT, et al. Echo-Doppler assessment of the biophysical properties of the aorta in children with chronic kidney disease. Pediatr Cardiol 2013; 34: 1218–1225.
83. Makulska I, Szczepanska M, Drozdz D, et al. Skin autofluorescence as a marker of cardiovascular risk in children with chronic kidney disease. Pediatr Nephrol 2013; 28: 121–128.
84. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003; 42: 1050–1065.
85. Aoun B, Lorton F, Wannous H, et al. Aortic stiffness in ESRD children before and after renal transplantation. Pediatr Nephrol 2010; 25: 1331–1336.
86. Cseprekal O, Kis E, Schaffer P, et al. Pulse wave velocity in children following renal transplantation. Nephrol Dial Transplant 2009; 24: 309–315.
87. Briese S, Claus M, Querfeld U. Arterial stiffness in children after renal transplantation. Pediatr Nephrol 2008; 23: 2241–2245.
88. Degi AA, Kis E, Kerti A, et al. Prevalence of obesity and metabolic changes after kidney transplantation: Hungarian pediatric cohort study. Transplantation Proc 2014; 46: 2160–2163.
89. Gardiner HM, Celermajer DS, Sorensen KE, et al. Arterial reactivity is significantly impaired in normotensive young adults after

successful repair of aortic coarctation in childhood. Circulation 1994; 89: 1745–1750.
90. Trojnarska O, Szczepaniak-Chichel L, Mizia-Stec K, et al. Vascular remodeling in adults after coarctation repair: impact of descending aorta stenosis and age at surgery. Clin Res Cardiol 2011; 100: 447–455.
91. Kenny D, Polson JW, Martin RP, et al. Relationship of aortic pulse wave velocity and baroreceptor reflex sensitivity to blood pressure control in patients with repaired coarctation of the aorta. Am Heart J 2011; 162: 398–404.
92. Ou P, Celermajer DS, Jolivet O, et al. Increased central aortic stiffness and left ventricular mass in normotensive young subjects after successful coarctation repair. Am Heart J 2008; 155: 187–193.
93. Niwa K, Perloff JK, Bhuta SM, et al. Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. Circulation 2001; 103: 393–400.
94. Tan JL, Davlouros PA, McCarthy KP, et al. Intrinsic histological abnormalities of aortic root and ascending aorta in tetralogy of Fallot: evidence of causative mechanism for aortic dilatation and aortopathy. Circulation 2005; 112: 961–968.
95. Niwa K. Aortic root dilatation in tetralogy of Fallot long-term after repair–histology of the aorta in tetralogy of Fallot: evidence of intrinsic aortopathy. Int J Cardiol 2005; 103: 117–119.
96. Niwa K, Siu SC, Webb GD, et al. Progressive aortic root dilatation in adults late after repair of tetralogy of Fallot. Circulation 2002; 106: 1374–1378.
97. Kim WH, Seo JW, Kim SJ, et al. Aortic dissection late after repair of tetralogy of Fallot. Int J Cardiol 2005; 101: 515–516.
98. Seki M, Kurishima C, Kawasaki H, et al. Aortic stiffness and aortic dilation in infants and children with tetralogy of Fallot before corrective surgery: evidence for intrinsically abnormal aortic mechanical property. Eur J Cardiothorac Surg 2012; 41: 277–282.
99. Saiki H, Kojima T, Seki M, et al. Marked disparity in mechanical wall properties between ascending and descending aorta in patients with tetralogy of Fallot. Eur J Cardiothorac Surg 2012; 41: 570–573.
100. Cheung YF, Ou X, Wong SJ. Central and peripheral arterial stiffness in patients after surgical repair of tetralogy of Fallot: implications for aortic root dilatation. Heart 2006; 92: 1827–1830.
101. Senzaki H, Iwamoto Y, Ishido H, et al. Arterial haemodynamics in patients after repair of tetralogy of Fallot: influence on left ventricular after load and aortic dilatation. Heart 2008; 94: 70–74.
102. Seki M, Kurishima C, Saiki H, et al. Progressive aortic dilation and aortic stiffness in children with repaired tetralogy of Fallot. Heart Vessels 2014; 29: 83–87.
103. Natarajan S, Heiss C, Yeghiazarians Y, et al. Peripheral arterial function in infants and young children with one-ventricle physiology and hypoxemia. Am J Cardiol 2009; 103: 862–866.
104. Sarkola T, Jaeggi E, Slorach C, et al. Assessment of vascular remodeling after the Fontan procedure using a novel very high resolution ultrasound method: arterial wall thinning and venous thickening in late follow-up. Heart Vessels 2013; 28: 66–75.
105. Myers KA, Leung MT, Terri Potts M, et al. Noninvasive assessment of vascular function and hydraulic power and efficiency in pediatric Fontan patients. J Am Soc Echocardiogr 2013; 26: 1221–1227.
106. Johansson S, Iliadou A, Bergvall N, et al. Risk of high blood pressure among young men increases with the degree of immaturity at birth. Circulation 2005; 112: 3430–3436.
107. Jarvelin MR, Sovio U, King V, et al. Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. Hypertension 2004; 44: 838–846.
108. Kaijser M, Bonamy AK, Akre O, et al. Perinatal risk factors for ischemic heart disease: disentangling the roles of birth weight and preterm birth. Circulation 2008; 117: 405–410.
109. Crump C, Sundquist K, Sundquist J, et al. Gestational age at birth and mortality in young adulthood. JAMA 2011; 306: 1233–1240.
110. McEniery CM, Bolton CE, Fawke J, et al. Cardiovascular consequences of extreme prematurity: the EPICure study. J Hypertens 2011; 29: 1367–1373.
111. Bonamy AK, Bendito A, Martin H, et al. Preterm birth contributes to increased vascular resistance and higher blood pressure in adolescent girls. Pediatr Res 2005; 58: 845–849.
112. Bradley TJ, Potts JE, Lee SK, et al. Early changes in the biophysical properties of the aorta in pre-adolescent children born small for gestational age. J Pediatr 2010; 156: 388–392.
113. Cheung YF, Wong KY, Lam BC, et al. Relation of arterial stiffness with gestational age and birth weight. Arch Dis Child 2004; 89: 217–221.
114. Lee SJ, Ahn HM, You JH, et al. Carotid intima-media thickness and pulse wave velocity after recovery from kawasaki disease. Korean Circ J 2009; 39: 264–269.
115. Ooyanagi R, Fuse S, Tomita H, et al. Pulse wave velocity and ankle brachial index in patients with Kawasaki disease. Pediatr Int 2004; 46: 398–402.
116. Cho HJ, Yang SI, Kim KH, et al. Cardiovascular risk factors of early atherosclerosis in school-aged children after Kawasaki disease. Korean J Pediatr 2014; 57: 217–221.
117. AlHuzaimi A, Al Mashham Y, Potts JE, et al. Echo-Doppler assessment of arterial stiffness in pediatric patients with Kawasaki disease. J Am Soc Echocardiogr 2013; 26: 1084–1089.
118. Hamaoka A, Hamaoka K, Yahata T, et al. Effects of HMG-CoA reductase inhibitors on continuous post-inflammatory vascular remodeling late after Kawasaki disease. J cardiol 2010; 56: 245–253.