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Review Article

Non-invasive Clinical Vascular Phenotyping in Children with Hypertension (Review)

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Abstract

Cardiovascular risk factors such as hypertension and obesity are rising in young children. Children with untreated hypertension are at high risk of cardiovascular complications and target organ damage later in life. As such, there is a need to identify feasible and reproducible techniques for vascular phenotyping of children and young people with hypertension and other chronic diseases. This will allow for the determination of which children are most at risk of early vascular dysfunction and for consideration of strategies to mitigate this risk. This narrative review describes current approaches to non-invasive clinical vascular phenotyping in the pediatric setting, with a particular focus on the assessment of endothelial function, through flow-mediated dilatation, venous occlusion plethysmography, and measurement of reactive hyperemia; identification of atherosclerosis through intima–media thickness measurements; and assessment of arterial stiffness through pulse wave analysis.

Key words: Blood pressure, carotid intima–media thickness test, flow-mediated dilatation, pediatric, pulse wave velocity

Introduction

The fetal origins of disease hypothesis was first proposed by Barker and colleagues in the 1980s and suggested that cardiovascular diseases (CVDs) originate through adaptations made by the fetus when it is compromised in some way *in utero* so that typical embryological development does not occur or there are imbalances in nutrient supply to the fetus or growth of the fetus.[1] Barker's landmark studies focused on the realization that infants born low birth weight had increased risk of ischemic heart disease later in life. This theory has since been corroborated by multiple studies which have shown associations between adverse fetal conditions and CVD. It appears that maternofetal stressors may result in epigenetic changes, leading to alterations in the sympathetic nervous system, renin-angiotensin system, and hypothalamic pituitary axis, with consequent modification to kidney, heart, and blood vessel function.[2] As such, over time the hypothesis has progressed to be called the Developmental Origins of Health and Disease model.

CVD remains the leading cause of death worldwide, representing over 30% of all deaths and 45% of non-communicable deaths.[3] Cardiovascular risk factors such as hypertension, obesity, and atherogenic lipid profiles are rising in young children, with this rise being attributed to pregnancy complications, genetic inheritance, and environmental risk factors in the early years. Children with untreated hypertension are at high risk of cardiovascular complications and target organ damage later in life.[4] Treatment of pediatric hypertension reduces the risk of atherosclerosis in adulthood, but there is some evidence to suggest that currently accepted thresholds for the definition of hypertension in children, do not take into account that the risk of target organ damage may be increased even at lower blood pressure (BP) levels.[4]

Given the association between early life influences and adult disease, it is essential to consider how to assess cardiovascular risk in children and young people using other non-invasive techniques, as this may lead to opportunities for risk mitigation and reduction in the public health burden of CVD in adulthood, as well as critical insights into the pathophysiology behind disease development. For example, a 20-year longitudinal study

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of children born preterm, demonstrated that the predominant underlying vascular phenotype in adult life differed according to maternal BP during pregnancy, suggesting that different risk stratification techniques would be required for these individuals to prevent future CVD.[5]

With an increasing focus on the vascular effects of childhood diseases, an abundance of research has studied non-invasive and acceptable methods to measure vascular function clinically in young people. New initiatives, including the Youth Vascular Consortium, have also recently been established to develop reference ranges for the most commonly used non-invasive vascular phenotyping techniques, on young people between the ages of 5 and 40 years.[6] The current reference ranges tend to be either from a single center or limited by small sample size, so collaborations such as these will ensure that these reference data are generalizable to the wider population. This narrative review will focus on these more commonly used methods for clinical vascular phenotyping, to assess vascular endothelial function, vascular remodeling, and arterial stiffness, and how they could be used to determine a clinical vascular phenotype in children. Although to date, there is insufficient evidence to support routine clinical use of the above methods in pediatric hypertension, large cohort studies, including work with the Avon Longitudinal Study of Parents and Children group, have shown that all of the techniques considered in this review are both feasible and reproducible in children and young people.[7] A summary of the techniques is given in Table 1.

Assessment of Vascular Endothelial Function

Flow-mediated dilatation

First described in a cohort of patients aged 8–57 years,[8] flow-mediated dilatation (FMD) is a technique which has been used as a surrogate marker of vascular health for nearly 30 years. FMD is determined by the change in brachial artery diameter caused by releasing a lower arm cuff that has been inflated to suprasystolic pressure for 5 min, with artery diameter being measured through ultrasound.[9] Cuff release triggers an endothelium-dependent nitric oxide (NO) response, which has been shown to be indicative of future vascular risk, as confirmed by meta-analysis, demonstrating a strong inverse relationship between FMD and increased cardiovascular risk.[9] This can be done manually using a traditional ultrasound machine and apparatus to keep the ultrasound probe in place above the brachial artery for the duration of the procedure or through a semi-automated device which uses B-Mode ultrasound to simultaneously capture longitudinal and cross-sectional views of the brachial artery.[10]

Several factors may influence endothelial function and as such recommendations in adults advise undertaking FMD on fasted participants, who have not undertaken strenuous exercise in the previous 24 h or taken any caffeine, tobacco, or drugs which may affect vascular status.[11] These issues are less likely to be prevalent in younger children, but must be considered in the assessment of adolescents. The use of nitroglycerin to assess endothelium-independent vasodilatation is also recommended in adults, but is not common practice in the pediatric setting. Repeated measures should be taken at the same time of the day to prevent potential diurnal variation and the readings should be undertaken on participants who are in the supine position and relaxed and through skilled operators. The technique can be technically difficult in children as they have to lie supine with their arm outstretched and under the ultrasound probe for 5 min without moving. The procedure cannot be reliably repeated immediately after an attempt because there may be some residual NO response.

Reference ranges for FMD have not yet been described in children. Observational studies have, however, shown sex differences in FMD in young children and adolescents, with males having lower median (range) FMD at 7.62% (7.33, 7.91) compared to age-matched females (8.31% [7.95, 8.66] ($P < 0.001$) and larger baseline artery diameter (2.96 mm [95% CI:2.92–3.00] vs. 3.24 mm [3.19–3.28]).[12] In addition, FMD declined with age throughout the cohort of 978 children (54% males, median age (range) 12.2 (6, 18) years), with more significant reduction post-puberty in males.[12] In adults, lower FMD levels are associated with vascular dysfunction.[8]

In disease states, FMD has been measured to date in children with type 1 diabetes, obesity, metabolic syndrome, rheumatic diseases, sickle cell diseases, Kawasaki disease, nephrotic syndrome, and moyamoya disease and lifestyle modifications and statin treatment have reported improved endothelial function as measured by FMD in children.[13]

Venous occlusion plethysmography

Although FMD is now considered to be the gold standard of the assessment of endothelial function, venous occlusion plethysmography is a technique which has been used to describe

Table 1: Summary of commonly used techniques for non-invasive vascular phenotyping in children

Focus of vascular assessment	Method	Vascular bed
Endothelial function	Flow mediated dilatation	Brachial artery
	Reactive hyperemia	Finger microcirculation
	Venous occlusion plethysmography	Forearm circulation
Atherosclerosis and vascular remodeling	Intima–media thickness	Carotid artery
		Aorta
Arterial stiffness	Pulse wave velocity	Carotid-femoral
Cardiac and vascular structure and function	Cardiac magnetic resonance imagining	Heart

vascular physiology since the early 20th century. In brief, this technique measures local vascular tone in response to an ischemic challenge by interrupting venous return from the area of study through cuff inflation below diastolic pressure, allowing for arterial inflow and venous emptying.[14] This can be done on two limbs at the same time and it can be combined with intra-arterial drug administration, if an invasive procedure will be tolerated by the child. A wrist cuff may be rapidly inflated above normal systolic pressure approximately 60 s before taking any measurements to exclude the effects of the hand's arteriovenous shunts from analysis. With increasing availability of ultrasound however, the set up for plethysmography can be more difficult and time consuming, as well as intimidating and difficult to tolerate for children. The procedure requires adherence to strict protocols, as factors such as cuff inflation time can significantly alter results. Although venous occlusion plethysmography has been demonstrated to be predictive of cardiovascular events in adults, variations in body habitus, forearm size, and blood flow mean that this technique is better suited for longitudinal studies measuring differences in blood flow in single patients, rather than comparison of distinct patient groups.

Reactive hyperemia index (RHI)

Measurement of RHI, through endothelial peripheral arterial tonometry (PAT), has potential to be useful in assessing endothelial function in a pediatric population because of its ease of use and automated analysis, reducing the effects of operator dependency and difficulty with engaging children in staying stationery for sufficient time to obtain accurate results. PAT is another plethysmographic method, which measures post-occlusive volume changes at the fingertip after an arterial occlusion of the upper arm of 5 min, through a thimble-shaped finger cap that applies pressure at the distal phalanx of the index fingers.[15] A close relationship between RHI and coronary dysfunction is described in adults, with reduced RHI values (typically <1.67) being used to define endothelial dysfunction in CVD and cerebrovascular disease.[15] RHI measurements have been found to be feasible and reproducible in both adolescents and school-aged children. There is increasing interest in this technique in children and to date, it has been described in children with acute lymphoblastic leukemia, obesity, juvenile dermatomyositis, and type 1 diabetes, although reference ranges have not yet been reported, and as such, it remains a research tool only. In addition, due to the disposable fingertip probes currently required for this technique, it is substantially more expensive than other non-invasive measures of endothelial function.

Assessment of Early Atherosclerosis and Vascular Remodeling

The pathological basis for CVD is arterial damage in the form of thickening and stiffness of the arteries. Atherosclerosis causes characteristic focal lesions in the intima of large and medium-sized arteries and can be identified through measurement of intima–media thickness (IMT).[16] In adults, carotid IMT (CIMT) is measured in the common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA) as standard. The carotid bulb and ICA are difficult to visualize in young children, however, so common practice is to measure only the CCA until late adolescence, albeit more advanced plaque formation usually occurs in the other 2 sites.[13,16]

IMT is closely related to BP, therefore in the general pediatric population correlates with age-related rises in BP, as well as height and body mass index (BMI).[17] IMT increases with age by approximately 0.003–0.004 mm per year in adolescence and 0.012–0.017 mm per year in adulthood (mean CIMT).[18] The morphological basis of IMT thickening is vascular smooth muscle cell hypertrophy and thickening of the extracellular matrix. In adults, CIMT varies with sex and ethnicity but these differences have not been identified in children as yet.[13]

In adults, increased CIMT is closely correlated with cardiovascular risk.[19-21] In children and adolescents, CIMT is increased in primary hypertension, end-stage renal disease, coarctation of the aorta, poorly controlled type 1 diabetes, and obesity. Fatty atherosclerotic streaks have been seen in children as young as 1 year.[22] Approximately 40% of children have some evidence of lipid deposition by the age of 16 years[23] and longitudinal studies have demonstrated that increased CIMT in childhood is likely to persist into adulthood.[13] Reference ranges for CIMT in children are available.[24]

Aortic IMT

Due to the anatomy of young children, CIMT measurements can be technically challenging. Therefore, when autopsy studies reported that initial atherosclerotic lesions are seen in the abdominal aorta rather than the carotid artery,[25] interest in aortic IMT (AIMT) developed, with early studies demonstrating this to be a feasible technique in children, correlating well with CIMT.[13] AIMT can be measured in fetuses and infants, enabling investigation of vascular remodeling from early in development. IMT increases can be observed in the aortas of human fetuses in response to the physiological rise in BP as gestation increases.[26] In addition, growth-restricted fetuses have been shown to have evidence of intimal–medial thickening detected in the abdominal aorta, identified on ultrasound as well as histological assessment of elastin structure, macrophage infiltration, and endothelial cell activation compared to non-growth-restricted fetuses.[27] The extent of fatty streaks in the abdominal aorta seems to correlate with the coronary arteries, suggesting that aortic atherosclerosis can be used as a proxy for coronary atherosclerosis.[28] Of note, although AIMT and CIMT are well correlated into adulthood, differences in AIMT were identified in younger children than CIMT, suggesting that it may be a more sensitive technique to identify vascular remodeling in younger populations.[29]

On a practical level, AIMT remains a research tool, with no available reference ranges. Detailed protocols have been published, however,[18] and it is an accepted and useful measure of early subclinical atherosclerosis, given that it is well tolerated,

with measurements only minimally affected by infant or environmental factors.[30]

Assessment of Arterial Stiffness

Arterial stiffness depends in part on smooth muscle tone. The shape of the arterial pressure waveform can, therefore, provide an objective assessment of arterial stiffness through pulse wave analysis.[31] Using an oscillometric device, measurements of pulse pressure (PP), central augmented pressure (AP), and augmentation index (AIx) are generated automatically. The central AP is the difference between the maximum systolic peak on the aortic pulse wave and the time to the reflected wave, as shown in Figure 1. The AIx is the AP/PP. The AIx is usually corrected to a heart rate of 75 as per previous studies (AIx 75).[13]

Pulse wave velocity (PWV) is regarded as a simple, robust, and reproducible way to measure arterial stiffness, with stiffer blood vessels resulting in a faster travel time and resultant higher PWV. It measures the speed of the pressure pulse, generated by ventricular ejection according to the geometric and elastic properties of the arterial wall, and is defined by the Moens–Korteweg equation, where E is Young's modulus of the arterial wall; h is wall thickness; p is blood density; and R is the arterial radius at the end of diastole: [13]

$$PWV = \sqrt{(Eh / 2pR)}$$

Carotid-femoral PWV is considered to be the gold standard assessment of arterial stiffness[32] and has been validated in children using applanation tonometry. Reference ranges are available, according to the age and height of the young person in different populations.[33,34] It is, however, subject to variation according to the accuracy of carotid-femoral distance measurements and differences in pressure application.

Studies have demonstrated that hypertension in childhood leads to increased PWV in adulthood.[35] Increased PWV has been reported in children with hypertension, diabetes, congenital heart disease, and obesity and may also adversely affect cognition in both adults and children.[35] Major predictors for PWV in childhood include sex, height, weight, BMI, diastolic BP, and heart rate demonstrating a need to consider ways to improve the modifiable risk factors such as BMI, BP, and HR early in life.[36]

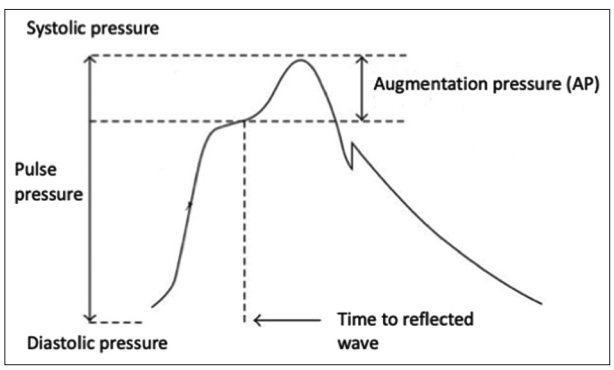

Figure 1: Pulse wave form as measured by pulse wave velocity

Cardiac Magnetic Resonance Imaging (MRI)

Cardiac MRI offers promise as an integrated approach to the assessment of both vascular and cardiac functions. Systemic vascular resistance, arterial stiffness, aortic flow, left ventricular mass and volumes, cardiac timings, and myocardial velocities can all be measured in a single sitting. Studies to date have examined MRI parameters in children with both renovascular hypertension and essential hypertension, and identified differences in the physiology between the two groups.[37] Cardiac MRI is also used routinely in clinical practice for girls with Turner syndrome and associated hypertension, to guide management.[38] However, it is an expensive procedure and requires access to state-of-the art MRI facilities, as well as expertise in analyzing and reporting the scans. In addition, MRI scans usually require general anesthetic in children between the ages of 6 months and 8 years, due to difficulty with image quality with any motion. As such, its utility in younger children is limited.

Circulating Cardiovascular Biomarkers

The identification of circulating cardiovascular biomarkers which can be identified non-invasively, through urine or saliva, will be of significant benefit in the pediatric setting for the assessment of vascular function. Hypertension is associated with endothelial dysfunction, inflammation, and oxidative stress and biomarkers such as endothelin-1, interleukin-6, C-reactive protein, and 8-hydroxy-deguanosine have all been measured successfully in the urine of children, with evidence of increased levels in children with hypertension and obesity.[39] In addition, miRNAs are short, non-coding RNAs, which act as post-transcriptional regulators by modifying target gene expression and may reflect molecular changes, which can be measured readily in urine and correlate well with other markers of cardiometabolic health in children.[40] Urinary metabolomics, therefore, offer the opportunity to identify relevant biomarkers on a large scale, with the benefit of urine samples being much easier and acceptable to obtain from pediatric patients compared to serum. Future studies should aim to determine whether these can be used in the clinical setting to guide risk stratification of children with hypertension.

Future Directions

Each of the tools considered in this review remains primarily for research purposes, with insufficient evidence to date to justify their routine clinical use. There is a need to focus future work on pooling international study data to confirm appropriate reference ranges for these techniques and to consider whether any of these methods could be used as a gold standard to identify subclinical vascular risk in at-risk patient groups, such as those with childhood-onset hypertension. The overall aim should be to reduce this risk in children, so as to prevent some of the significant CVD seen in adulthood. Longitudinal studies assessing the change in vascular parameters with age are also required.

Conclusions

Non-invasive vascular phenotyping is an area of increasing interest in pediatrics. Atherosclerosis has a long subclinical course, from the fetal period, where initial functional and structural arterial changes can be identified through to adulthood, where advanced atherosclerotic lesions result in cardiovascular morbidity and mortality. There has been some debate regarding the responsibility of pediatricians to prevent adult disease, but differences in endothelial function and arterial stiffness can be measured accurately in young children. As such, the methods described in this review should be considered in studies assessing vascular risk in the pediatric setting. Each technique has its own challenges within the pediatric population and may need to be adapted to ensure tolerability for the age and stage of the child being assessed.

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