Abnormalities of vascular structure and function in pediatric hypertension

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Abstract Hypertension is associated with adverse cardiovascular (CV) events in adults. Measures of vascular structure and function, including increased carotid intima–media thickness (cIMT) and elevated arterial stiffness predict hard CV events in adulthood. Newer data suggest that abnormalities in target organ damage are occurring in adolescents and young adults with high blood pressure. In this review, we discuss the techniques for measuring vascular dysfunction in young people and the evidence linking blood pressure levels to this type of target organ damage.

Keywords Pediatric · Hypertension · Carotid artery · Arterial stiffness

Introduction

High blood pressure (BP) in adults is associated with both hard cardiovascular (CV) events [1] and with measures of target organ damage, such as increased left ventricular mass (LVM), carotid intima–media thickness (cIMT), and arterial stiffness [2–4]. Since risk for CV events increases in a linear fashion at higher levels of BP without a threshold effect (i.e., a clear cut-point at which lower levels of BP are “safe”) [5], evaluation of these intermediate measures of vascular structure and function, which are associated with hard events, has gained increasing use [6]. In this review, we discuss the

evidence relating to BP levels in young people with vascular target organ damage.

Why should we measure vascular function in young people?

Cardiovascular diseases (CVD) account for one third of all-cause mortality throughout the world, even in sub-Saharan Africa [7]. By 2030, 40.5 % of the US population are projected to have some form of CVD, with total direct medical costs of CVD projected to triple, from \$309 billion to \$834 billion by 2030 [8]. Much of this increase in CVD is due to hypertension (HTN), which has a prevalence 28 % in women and 35 % in men worldwide [7]. Although the prevalence of HTN in children is much lower, there was still an increase in the prevalence of elevated BP in the US from the late 1980s to the early 2000s coincident with the onset of the obesity epidemic. Since the Bogalusa Heart Study demonstrated increased atherosclerosis at autopsy in adolescents with hypertension [9] attention to the diagnosis of HTN and evaluation of subsequent BP-related damage in young people is critical in preventing future CV events.

How do we measure vascular function in pediatric patients and what are the data relating BP to vascular abnormalities?

Vascular testing can include measures of vascular structure, arterial stiffness, and endothelial function. These tests are related, but measure different properties of the arterial tree. They are also affected by risk factors in a non-uniform fashion. In addition, there are also differences in the time-course for improvement with interventions. Therefore, if possible, vascular

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assessment should include a combination of techniques applied to a variety of vascular beds.

Vascular structure

Ultrasound (“B-mode” imaging) is the primary method used to measure vascular structure and the carotid artery is the most widely imaged, as it is the most accessible and easy to measure, and relates to CV events in adults [10]. The combined intima and media thickness (IMT) is reported because ultrasound does not allow for delineation of the intima and media. The interface changes with changes in gain on the device, although there are techniques in development that may overcome this problem [11]. The femoral artery can also be evaluated, but is more difficult to image and correlates strongly with the carotid, thus offering little advantage [12]. The abdominal aortic thickness can also be measured and may be an early reflection of diseases such as diabetes and high cholesterol in younger subjects, but requires additional equipment (curved array transducer). This technique may be less acceptable to patients owing to the discomfort of the imaging protocols and the requirement that they are performed in the fasting state because of the difficulty of imaging the aorta through a fluid- and air-filled bowel [13].

In the 1990s, the first studies relating pediatric BP levels to vascular damage found that BP measured as young as 9 years of age predicted higher cIMT as a young adult [14]. Later IMT was directly measured in healthy adolescents and BP was found to be an important correlate of thicker IMT [15]. A similar study in healthy German Caucasian children found thicker carotid and femoral IMT in young people who had systolic BP (SBP) in the top 10th percentile of the distribution [16]. Similarly, in a larger bi-racial (black–white) cohort, thicker IMT was found in subjects with pre-hypertension at the 90th percentile of BP [17]. Unfortunately, even thicker IMT is found in young people with clusters of CV risk factors (HTN, obesity, and dyslipidemia) compared with patients with isolated HTN without other risk factors [18, 19]. It also appears that the degree of BP elevation is important. Lande et al. [20], found that IMT correlated with higher daytime SBP index (measured with ambulatory BP monitoring), which indicates more severe HTN. Other investigators have related 24-h ambulatory BP monitoring measures to IMT, including a study of young people with type 1 diabetes mellitus where adolescents with reduced nocturnal BP dipping were found to have a thicker IMT [21]. Children with chronic kidney disease (CKD) have also been found to have a thicker cIMT than age-matched controls [22]. Severity of kidney disease appears to be important as well, as children on dialysis had higher IMT than patients with milder chronic renal insufficiency (Fig. 1). Of interest, there was a graded increase in BP from controls to chronic renal insufficiency to dialysis

Fig. 1 Increased carotid thickness in pediatric patients with chronic kidney disease ($N=93$, mean age 14 years) $p \leq 0.05$: *compared with normal values; †compared with chronic renal insufficiency (CRI)[22]. cIMT carotid intima–media thickness

patients—only calcium $\times$ phosphate product was an independent predictor of cIMT, but not BP [22].

Arterial stiffness

Arterial stiffness is important to evaluate as, similar to cIMT, stiffness predicts CV events, both in high-risk adults with CKD [23] and in healthy adults. In fact, the Framingham Heart Study found that elevated pulse wave velocity ($PWV \geq 11.8$ m/s) was associated with a 48 % increase in the risk for a CV event over only 7.8 years of follow-up [4]. Furthermore, adult data would suggest that abnormalities in arterial stiffness may precede the development of HTN, rather than be a consequence of higher BP levels [24]. However, measurement can be challenging because the arterial wall possesses properties that make it behave somewhat like an elastic solid, but also as a viscous liquid [25]. Therefore, a variety of techniques have been developed.

During imaging for the measurement of cIMT, M-mode evaluation of the common carotid artery provides high-quality images of the maximal (systolic) and minimal (diastolic) diameters for the calculation of carotid stiffness (Fig. 2). There are a variety of calculations that describe slightly different parameters of arterial stiffness [6]. Using this technique, Litwin et al. [26] demonstrated greater elastic modulus and beta stiffness index in adolescents (mean age 14.5 years) who were newly diagnosed with HTN compared with normotensive controls. Unfortunately, in a later study, increased carotid stiffness was also found in pre-hypertensive young people well before progression to sustained HTN [17]. Similar to data on IMT, investigators also demonstrated higher carotid stiffness in dialysis patients compared with both subjects with

Fig. 2 Carotid B-mode and M-mode ultrasound for the measurement of carotid stiffness

mild CKD and normal age-matched controls [22]. After renal transplant, these abnormalities in carotid stiffness remain and correlate with higher BP measured with ambulatory monitoring [27]. In addition to M-mode evaluation of ultrasound images, radiofrequency wall-tracker devices (“A-mode”) have also been developed and applied to the brachial artery. In a large cohort of adolescents, Whincup et al. [28] found that brachial artery distensibility declined in a curvilinear fashion with increasing levels of diastolic blood pressure (DBP).

Non-ultrasound methods for evaluating arterial stiffness have also been developed, such as a cuff-based pressure device that measures resting brachial artery distensibility. Similar to the A-mode ultrasound technique, brachial distensibility falls across the BP distribution (Fig. 3) from normo-, to pre-, to true-hypertensive subjects [17]. This technique has also demonstrated abnormal brachial artery function in young people with obesity and type 1 and type 2 diabetes mellitus, and BP was found to be an

independent determinant of distensibility, even after adjusting for other CV risk factors [29, 30].

Pulse wave velocity measures the speed at which the bolus of blood travels along the arterial tree and is one of the most robust measures of arterial stiffness because of its strong relationship to hard CV events [4]. PWV is often measured with pressure sensors placed on a proximal (usually carotid) and then distal (usually femoral) artery. There is a large body of evidence demonstrating case-control differences in PWV in adults, with an increasing amount of information on pediatric diseases, including obesity-related insulin resistance [31], type 1 [30] and type 2 diabetes mellitus [29], acute post-streptococcus glomerulonephritis [32], and CKD (Fig. 4) [33]. As with other measures of arterial stiffness, adolescents with pre-hypertension have a higher PWV (stiffer vessel) compared with normotensive young people [17, 34] and this relationship held true regardless of the level of adiposity [35]. BP has a strong influence on PWV, as seen in the observation

Fig. 3 Decline in brachial artery distensibility with increasing systolic blood pressure (SBP) [17]. $R^2=0.27$, $p\leq 0.001$; solid line mean, dotted lines 95 % confidence intervals

Fig. 4 Higher pulse wave velocity (*PWV*) in young people with chronic kidney disease (*CKD*) [33]. * $p \leq 0.05$ for differences among groups

that patients with successful repair of coarctation of the aorta had higher PWV if they had HTN on ambulatory monitoring [36] or had an exaggerated BP response to exercise [37]. PWV is also higher in patients after kidney [38] or heart transplantation [39], or in patients with systemic lupus erythematosus [40] compared with controls, and in each study PWV correlated directly with BP level. PWV has also been related to CV risk factors in healthy young people, as Japanese studies measuring brachial-ankle PWV demonstrated stiffer vessels with higher BP [41–43]. However, it should be noted that the brachial-ankle PWV technique includes assessment along the brachial artery, which is a medium muscular artery and may not relate to long-term CV risk in the same fashion as carotid–femoral PWV does. Lifestyles that affect BP are also known to influence PWV. Edwards et al. demonstrated higher PWV in young people with lower levels of physical activity, measured with accelerometry [44].

Another measure related to arterial stiffness is the augmentation index (AIx), which incorporates features of central arterial stiffness, but is predominantly affected by wave reflections. Similar to PWV, this is measured with pressure tonometry. The vasculature is not an open-ended system in that blood does not, under normal circumstances, leave the

arteries, but the pulse hits various branch points in the body and waves are reflected back to the heart. Therefore, the cardiac afterload, or force against which the heart must pump, is a summation of the outgoing and reflected wave [45]. To understand these forces, AIx is calculated as the difference in pressure between the main outgoing cardiac pulse wave and the incoming reflected wave as a percentage of pulse pressure normalized to a heart rate of 75 beats per minute. Flexible vessels return the wave, slowly arriving late in systole or early in diastole. Stiff vessels return it quickly, arriving in early systole, thus “augmenting” the central aortic pulse pressure. This increased pressure increases demand upon the heart and reduces the area under the curve of the pulse wave during diastole, thus reducing the driving pressure for coronary filling [25]. The increase in demand and decreased blood supply are the likely explanations for the finding that a 10 % increase in AIx resulted in a relative risk for total CV events of 1.318 (95 % CI 1.093–1.588) in a meta-analysis of adult studies [46]. Pediatric studies have demonstrated increased AIx in subjects with both HTN and pre-hypertension compared with normotensive young people [17], obesity with insulin resistance [31], type 2 diabetes mellitus [29], and young people with low levels of physical activity measured with accelerometry [44]. Children with CKD have higher AIx than healthy controls, with patients on hemodialysis demonstrating stiffer vessels than those on peritoneal dialysis (Fig. 5) [45]. Although vitamin D level was an independent determinant of AIx in this study, surprisingly, calcium–phosphorus product was not [45]. Factors other than arterial stiffness, however, may affect AIx, including distal endothelial function. Therefore, the measure has greater biological variability and lacks as clear a biological significance as PWV.

Ambulatory arterial stiffness index (AASI) is another parameter calculated from a 24-h BP monitor as 1 minus the slope of the regression of the 24-h SBP readings on the DBP readings. An advantage of AASI is that it can be obtained without specialized equipment, and it may be an indicator of ventricular–arterial coupling as it is dependent upon both cardiac function (cardiac output) and arterial function (pulse pressure) [47].

Fig. 5 Elevated augmentation index (AIx) in children with chronic kidney disease (*CKD*). $N=62$, mean age 15 years [45]

However, since it is dependent on rate and systemic vascular resistance, it is not an independent reflection of arterial function, which is an important limitation [48]. Regardless, utility of the parameter is suggested by observations that AASI is elevated in children and young adults with primary HTN and secondary to repaired coarctation of the aorta [49]. AASI was also elevated in children with type 1 diabetes mellitus and concomitant hypertension compared with healthy controls or non-hypertensive diabetic young people [50].

Endothelial function

Endothelial function measures the ability of the endothelium to respond to stress, in contrast to arterial stiffness, which describes the visco-elastic nature of the arterial wall [25]. The current gold standard for the measurement of endothelial function is ultrasound-based brachial flow-mediated dilation (FMD). FMD is useful to measure, as adults with reduced FMD and metabolic syndrome are at a greater risk for CV events [51]. However, brachial FMD is challenging to measure reproducibly, requires training and rigorous quality controls, and may not be feasible in younger children owing to the discomfort of inflating a BP cuff on the forearm for 5 min to induce the ischemic stimulus [6]. For this reason, fewer pediatric data are available. Early studies showed that children with CKD had lower FMD compared to age-matched controls [52]. Later studies found a graded decrease in endothelial function with severity of renal impairment, highest FMD in healthy adolescents, and a graded decline in patients who had post-renal transplant status, with lowest levels in young people on dialysis [53]. In fact, FMD appears to be acutely impaired directly after dialysis, possibly because of increased sympathetic nervous system outflow in response to a decreased effective circulating volume [54].

Non-ultrasound methods for the measurement of endothelial function are also available. One device (EndoPAT, Itamar Medical, Caesarea, Israel) uses finger cuffs placed on the control and test arm (where the BP cuff is inflated) and a technique called peripheral arterial tonometry to measure reactive hyperemic index (RHI), a parameter related to FMD [55]. Using this technique in children aged 8.8 years, Aggoun et al. [56] found that FMD correlated negatively with mean 24-h ambulatory SBP and DBP. Since younger children may not tolerate ischemic stimulus, laser flow Doppler (LFD) with a heating stimulus can also be used to measure endothelial function. Microvascular response to local heating is reduced in adults with hypertension [57]. Studies of pediatric patients with hypertension have not yet been conducted. However, reduced LFD response has been found in young people with type 1 diabetes mellitus who were normotensive compared with controls [58] and diabetics who had higher levels of BP than controls [59], suggesting its usefulness as an endothelial function measure in pediatric diseases.

Another method for the measurement of endothelial function is venous plethysmography. In this technique, a stretchy “strain gauge” strap is placed around the mid-forearm, and inflatable BP cuffs are placed on the upper arm and the wrist. The cuffs are inflated just high enough to obstruct venous outflow, while allowing normal arterial inflow. This leads to an increase in limb volume (circumference) proportional to the rate of arterial inflow. The device records the volume change in electrical resistance units. One advantage is that this technique avoids the confounding effect of systemic counter-regulatory systems (such as an increase in heart rate with administration of peripheral vasodilators) by confining study to the limb. Furthermore, one can design mechanistic studies by infusing specific agonists/antagonists. However, these drug protocols require placement of a micro-dialysis catheter that is semi-invasive. Furthermore, the device only evaluates resistance vessels, not the conduit vessels (such as the aorta) where the first development of atherosclerosis likely occurs [60]. The device can also be used with other types of stimuli that are non-invasive. In one study of 10-year-old children, obese children had lower forearm blood flow and vascular conductance with handgrip and mental stress testing than lean controls. Furthermore, mean arterial pressure response during these stress tests was exaggerated in obese compared with lean young people [61].

Venous function

Venous dysfunction is known to contribute significantly toward reducing quality of life in patients with a single ventricle after a Fontan operation. These patients have thicker veins [62], which are dysfunctional, leading to higher rates of venous reflux and venous insufficiency [63]. Whether hypertension leads to similar types of venous abnormality is not clear. Most studies show no difference between hypertensive patients and controls in terms of venous function [64, 65] and no change in venous outflow with administration of felodipine [66], but others have reported higher venous pressure in the arms of patients [67] and greater reduction in venous compliance in response to lower-body negative pressure [68]. To our knowledge, no similar studies have been conducted in young people with hypertension.

Why should we worry about vascular dysfunction?

Although “hardening of the arteries” is a popular lay term for atherosclerosis, people do not die of vascular dysfunction, rather, they experience morbidity and mortality from target organ damage caused by various factors, including increased arterial stiffness and endothelial dysfunction. Therefore, it is significant that pediatric studies have demonstrated evidence for a direct relationship between arterial parameters and

measures of target organ damage. Since a thicker vessel is likely to impart higher cardiac afterload (the force against which the heart must pump), it is not surprising that Sorof et al. [19] demonstrated that young people with thicker carotid arteries had greater LVM. When a global arterial stiffness index was calculated from multiple vascular parameters reflecting both peripheral and central arterial stiffness and wave reflections, the “Global Stiffness Index” (GSI) was an independent determinant of LVM in adolescents, even after adjusting for traditional CV risk factors (Fig. 6) [69]. Similarly, GSI was linearly related to diastolic function (E'/A' ratio) in this cohort (unpublished data). These observations suggest that treatments to improve vascular function in young people may be important in preventing future CV events such as heart failure.

What should we do to improve vascular function?

Measurement of vascular function is an important step in refining the level of risk for future hard CV events. Ideally, however, treatments could be developed to alter the natural history of CVD in high-risk individuals. To that end, various studies have investigated the potential for improving vascular parameters with both lifestyle and drug therapies. Large epidemiological studies including the Bogalusa Heart Study [70] and the Young Finns study [71], were the first to demonstrate that lower levels of CV risk factors in young people were associated with lower cIMT as an adult. In fact, in a combined analysis of both cohorts, if metabolic syndrome present in childhood resolved by adulthood, the IMT was the same as individuals with low risk factors at both time points [72]. Furthermore, high consumption of fruits and vegetables across the lifespan was associated with lower PWV (lower stiffness) as an adult in the Young Finns study [73]. These data strongly support the hypothesis that primordial prevention, or the prevention of acquisition of CV risk factors [74], namely obesity, should be the population-based approach to reducing the incidence of CVD. Data supporting this

premise include recent studies demonstrating that meeting a greater number of ideal CV health metrics is associated with lower PWV and AIx in young people with type 1 diabetes mellitus [75]. Other pediatric studies have shown regression of IMT in children after weight loss [76] and improvement in forearm blood flow (by venous plethysmography) in young people undergoing a diet and exercise program [61], with both studies demonstrating a concomitant drop in BP levels. Primary prevention in young people (treatment of CV risk factors) is also effective, as demonstrated by regression of IMT with statins in young people with familial hypercholesterolemia [77]. Dietary modification may also be useful, as a study that adapted the Dietary Approaches to Stop Hypertension diet for teens with prehypertension and hypertension showed improvement in BP and normalization of FMD after 6 months of intensive diet modification (Fig. 7). Unfortunately, a year after the end of the intervention, poor dietary patterns returned and FMD declined (unpublished data). Secondary prevention in pediatrics (aggressive treatment of high-risk young people) may also improve vascular function. Both carotid thickness [78] and stiffness [53] improve after kidney transplant in young people with chronic CKD. Resolution of obstructive sleep apnea after adenotonsillectomy results in improvement of BP and LFD response [79]. Unfortunately, there are no randomized clinical trials demonstrating improvement of vascular parameters with anti-hypertensive drugs. There are limited data on the use of supplements with varied results. Some studies suggest that folic acid, but not L-arginine, a nitric oxide donor, might result in improved FMD in young people with kidney disease [80]. Another study, conducted in pediatric heart transplant patients, found improvement in FMD with acute intravenous administration of L-arginine [81]. Another found improved FMD with folate, or vitamin B6, in young people with type 1 diabetes mellitus [82]. High-dose vitamin C improved RHI in patients with single-ventricle congenital heart disease after Fontan palliation [83]. Unfortunately, all of these studies are small single-center studies and none has been replicated on a large scale.

Fig. 6 Relationship between arterial stiffness and left ventricular mass index (LVM) (mean and 95 % confidence interval). $N=670$, mean age 18 years. $R^2=0.52$; p for slope differs from zero ≤ 0.001 . Reproduced from Urbina et al. [69], used with permission

Fig. 7 Improved flow-mediated dilation (FMD) in young people with hypertension (HTN) after 6 months of the DASH-4-Teens Diet, $p=0.05$. $N=64$, mean age 15 years

Future directions

Normative data across age, body size, and race/ethnicity for measures of vascular structure and function are lacking. Some large epidemiological studies measuring PWV included a few children [84–87] and other small cross-sectional studies included both healthy young people and pediatric subjects with a variety of conditions, such as obesity and diabetes [29] or hypertension [17]. However, there is lack of consistency among techniques such that the “normal” values must be interpreted only for the specific device used and the particular patient population. There are also insufficient data to develop z-scores to adjust raw values for differences in body size or maturation. Finally, longitudinal data across adolescence are lacking. One study found an increase in PWV over 3 years in males but not females ($p \leq 0.0001$) [88]. Clearly, more studies are needed to evaluate the determinants of accelerated vascular aging in young people.

Summary

There is clear evidence that vascular thickness and stiffness increase and endothelial function decreases in young people with CV risk factors, such as hypertension. Abnormalities in vascular parameters predict hard CV events in adults. Luckily, lifestyle modifications show promise in improving arterial structure and function. However, much work remains to be done, including:

1. The collection of more normative data across age, sex, and race/ethnicity
2. Larger observational studies to refine determinants of healthy of abnormal vasculature across a variety of pediatric conditions

3. Large, robust, randomized clinical trials to demonstrate improvement in arterial thickness, stiffness, and endothelial function in young people

Since F.A. Mahomed first declared in the 1800s “by his pulse you shall know him” [89], we have recognized the importance of vascular measures as a window to overall health. Hopefully, new research will develop effective and safe therapies for pediatric patients, and thus reduce the burden of CV diseases around the world.

Key summary points

1. Vascular structure and function predict hard CV events in adults.
2. Abnormalities in vascular structure and function can be identified in asymptomatic young people with hypertension.
3. Complete vascular evaluation includes measures of structure (i.e., cIMT), arterial stiffness (i.e., PWV) and endothelial function (i.e., FMD).
4. Stiffer arteries are associated with higher LVM.
5. Lifestyle modifications have been shown to improve vascular parameters in young people.

Questions (Answers are provided following the reference list)

1. Which vascular parameter predicted future CV events in the Framingham Heart Study?
 - a) cIMT
 - b) PWV
 - c) AIx
 - d) FMD
 - e) Venous plethysmography
2. Adolescents with chronic renal insufficiency have a thinner carotid artery than patients requiring dialysis.
 - a) True
 - b) False
3. Brachial flow-mediated dilation is a robust measure of arterial stiffness.
 - a) True
 - b) False
4. Which measure of arterial stiffness can be calculated from 24-h ambulatory BP recordings?
 - a) AIx
 - b) FMD

- c) AASI
- d) LFD
- 5. Renal transplant has led to improvement in which of the following vascular parameters?
 - a) cIMT
 - b) LFD
 - c) AIx
 - d) FMD
 - e) Venous plethysmography

Conflict of Interest The authors declare that they have no conflict of interest.

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Answers

1. B
2. A
3. B
4. C
5. A