Arterial Stiffness and the Kidney

Arterial Stiffness in Children: Pediatric Measurement and Considerations

Jonathan D. Savant^a Susan L. Furth^{a, b} Kevin E.C. Meyers^a

^aDivision of Nephrology, Department of Pediatrics, The Children's Hospital of Philadelphia, and ^bDepartment of Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pa., USA

Key Words

Arterial stiffness · Atherosclerosis · Children · Pulse wave analysis · Pulse wave velocity

Abstract

Background: Arterial stiffness is a natural consequence of aging, accelerated in certain chronic conditions, and predictive of cardiovascular events in adults. Emerging research suggests the importance of arterial stiffness in pediatric populations. **Methods:** There are different indices of arterial stiffness. The present manuscript focuses on carotid-femoral pulse wave velocity and pulse wave analysis, although other methodologies are discussed. Also reviewed are specific measurement considerations for pediatric populations and the literature describing arterial stiffness in children with certain chronic conditions (primary hypertension, obesity, diabetes, chronic kidney disease, hypercholesterolemia, genetic syndromes involving vasculopathy, and solid organ transplant recipients). **Conclusions:** The measurement of arterial stiffness in children is feasible and, under controlled conditions, can give accurate information about the underlying state of the arteries. This potentially adds valuable information about the functionality of the cardiovascular system in children with a variety of chronic diseases well beyond that of the brachial artery blood pressure.

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What Is Arterial Stiffness?

The capability of conduit arteries to accommodate large pressure ejections from the heart during systole and to distend and store blood which can be perfused to tissues and organs during diastole is largely mediated by the elastic properties, or compliance, of the arterial system. Stiffer arteries require greater force to expand and accommodate blood flow,

Susan Furth, MD, PhD
Division of Nephrology, The Children's Hospital of Philadelphia
3401 Civic Center Blvd
Philadelphia, PA 19104 (USA)
E-Mail furths@email.chop.edu

Fig. 1. Mechanisms of arterial stiffness. Adapted from Zieman et al. [3]. AGE = Advanced glycation end products; I-CAM = intracellular adhesion molecule; MΦ = macrophages; MMP = matrix metalloproteinases; NaCl = sodium chloride; TGF-β = transforming growth factor-β; VSMC = vascular smooth muscle cell.

and this leads to increased work load for the heart which, over time, can lead to left ventricular hypertrophy. This stiffening is due to changes in structural and cellular components of the vessel wall and occurs through several complex, interactive mechanisms, such as the regulation of extrinsic factors and hemodynamic forces (fig. 1). A detailed discussion of these mechanisms is beyond the scope of the present review and is well described in the literature [1–4]. Briefly, vascular stiffening is a complex interaction of hemodynamic factors (e.g., collagen, elastin, metalloproteinases, etc.) and intraluminal influences (e.g., neuroendocrine signaling, sodium intake, glucose regulation, etc.). Arterial stiffening is a natural consequence of aging, but a number of disease states have been shown to contribute to arterial stiffening, such as hypertension, chronic kidney disease (CKD), obesity, and diabetes. For instance, in individuals with CKD, arterial stiffening has multiple contributing factors, such as arterial calcifications, systemic inflammation, malnutrition, vitamin deficiencies, endothelial dysfunction, and bone activity contributing. Calcium and phosphate balance also contributes to the development of aortic stiffness.

How to Measure Arterial Stiffness?

There are many different indices of arterial stiffness. These include functional measures such as pulse wave velocity (PWV), pulse wave analysis (PWA), ambulatory arterial stiffness index (via 24-hour ambulatory blood pressure monitoring), and assessment of endothelial

dysfunction (via flow-mediated dilation). In this review, we will focus on PWV and PWA, as most data in children to date have been gathered using these modalities.

PWV measures the speed of the pressure pulse made by the heart as it circulates through the blood vessels and is simply calculated by dividing the distance travelled by the time it takes to travel the said distance. Stiffer blood vessels result in a faster travel time, and, thus, in a higher PWV. A 2006 expert consensus document from the European Society of Cardiology states that ‘the measurement of PWV is generally accepted as the most simple, non-invasive, robust, and reproducible method to determine arterial stiffness’ [5], and the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for the management of arterial hypertension recommend the assessment of PWV in clinical practice [6].

There are several different modalities to ascertain PWV, such as using applanation tonometry, oscillometry, Doppler echocardiography, or MRI, and each is associated with its own strengths and weaknesses. As not all arteries are equal in function, size, location, or stiffness, PWV can vary depending on the segment of the arterial trunk being assessed. In adults, the ‘gold standard’ for the noninvasive assessment of arterial stiffness is carotid-femoral PWV (cfPWV) [5]. While other methods of assessing aortic PWV have been validated, and largely show comparable results [7–9], in this paper, we will primarily focus on cfPWV as measured by applanation tonometry, unless otherwise specified.

PWA is an indirect measure of arterial stiffness, which can supplement PWV by providing information regarding wave reflection. While cfPWV measures central (aortic) arterial stiffness, PWA is an amalgam measure of central and peripheral arterial stiffness. Peripheral reflected pulse waves return to the aortic root rapidly via stiffer arteries, which can augment systolic pressure leading to increased central pulse pressure. Augmentation pressure is defined as the difference between the second and the first systolic peaks, while the augmentation index (Aix) is the ratio of augmentation pressure to pulse pressure expressed as a percentage (fig. 2). As with PWV, a higher Aix is indicative of stiffer arteries.

Importance/Implications of Arterial Stiffness

In a Dutch cohort study of 381 patients with an onset of end-stage renal disease (ESRD) between 0 and 14 years of age, cardiovascular disease accounted for 36% of deaths in patients with a functioning graft [10]. However, more recent data from the Netherlands suggest that cardiovascular outcomes in children after renal transplantation may be improving [11]. This may be because more attention is being paid to the cardiovascular system, especially to a better control of hypertension. It is time, however, to move on to a more comprehensive evaluation and management of the cardiovascular system in children with chronic renal disease. Arterial stiffness is an important predictor of future cardiovascular events, particularly in adults [12–15]. Less direct evidence of hard outcomes exists in children. In adults, models incorporating PWV measurements demonstrate that 1 SD increment in PWV is equivalent to 10 years of aging [16].

Aortic PWV is increasingly recognized as an important component in the determination of cardiovascular risk in CKD and ESRD populations [17]. Aortic stiffness has independent predictive values for all-cause and cardiovascular mortality in general populations and in adults with ESRD [12, 18]. A number of studies suggest that there is a relationship between arterial stiffness and decreased glomerular filtration rate and that it is predictive of kidney disease progression [5, 19–21]. Carotid-femoral PWV is, in turn, a direct measure of aortic stiffness and is the gold standard for its evaluation in clinical and epidemiological studies [22]. PWV has proven to be a useful tool to assess and follow arterial stiffness in CKD patients [23].

Fig. 2. Comparing PWA of a healthy (a) versus CKD stage III (b) 9-year-old male. Collected by the SphygmoCor device (AtCor Medical Inc.). AP = Augmentation pressure; PP = pulse pressure.

The demonstration of PWV abnormalities and their incorporation into risk estimates for reaching ESRD in children, or, in longer-term follow-up, the risk of death or cardiovascular events could importantly target high-risk populations for intervention strategies to decrease the morbidity of cardiovascular disease in early CKD.

Challenges of Measurement in Children

Although there are different methods/techniques to assess arterial stiffness, many have not been standardized for children. A number of challenges exist, including training requirements, as high-quality, reproducible, and reliable measures require a great deal of individual experience and expertise. There is also a lack of pediatric validation studies comparing invasive measures such as cardiac catheterization and noninvasive measures such as cfPWV, primarily due to the ethical concerns involved with invasive studies in children solely for research purposes [24]. Normative values do exist for cfPWV in children which makes this measure in children more appealing [25].

While cfPWV as assessed by applanation tonometry is the most commonly used measure of arterial stiffness, there are limitations. In some patients, especially in younger children, pulse acquisition via applanation tonometry can be difficult. When measuring the pulse wave at two different sites (i.e., carotid and femoral), it is important that the heart rate does not differ significantly during the acquisition phases. Therefore, ensuring that the patient remains still throughout, and has had sufficient time to rest before initiating the measurement, is imperative. However, even if the patient is cooperative, it can be more difficult to maintain a sufficiently strong signal from the smaller arteries in younger children. Similarly, obesity can

mask the pulse site, particularly the femoral artery, and require the application of greater pressure from the operator. Some patients may be embarrassed or uncomfortable with exposing their femoral artery, which may artificially increase the heart rate. Care should be taken to sufficiently explain the importance and reason for the procedure and drape them with a blanket. Standard conditions should also be observed, including the temperature of the room, abstinence from caffeine or vasodilators, and the time of day, among others [5].

Additionally, and this is true with all PWV measures with multiple pulse acquisition sites, the lack of standardization in distance measurement is problematic. A study comparing invasively measured PWV with noninvasive cfPWV using five different methods of distance measurement found that the best agreement was achieved subtracting the carotid-suprasternal notch distance from the suprasternal notch-femoral distance [26]. They also found a mean PWV difference of 2.9 m/s using the longer measurement of the direct carotid-femoral distance, highlighting the importance of standardizing methodologies, and reporting specific distance measurements used in publications to facilitate interpretation. This is important clinically as well, as the ESH/ESC guidelines from 2007 recommended a cutoff PWV value in adults of 12 m/s for identifying alterations of aortic function, using a measurement of the carotid-femoral distance [27]. However, given that the distance between the carotid and femoral arteries along the body surface are greater than the direct route inside the body along the aortic trunk, recent guidelines suggest applying a correction factor of 80% if measuring the distance this way, giving a new cutoff of 10 m/s ($0.8 \times 12 = 9.6$) [6, 28]. There are no similar suggested cutoff values of clinical significance for children, where PWV values are much lower. For instance, if a 7-year-old female with a height of 127 cm had a measured cfPWV of 5.5 m/s, she would be above the 95th percentile (fig. 3).

Obesity can also artificially elevate the distance measurement between the carotid and femoral arteries when measured along the body habitus. Townsend et al. [20] found that this distance was elevated with increasing waist circumference, and they used a regression-based method to adjust for this difference in analysis. Others have attempted to account for waist circumference by measuring between the two sites to the side of the body, avoiding the waist altogether. Offsetting these limitations is that training operators can be relatively simple, the procedure is usually well tolerated and feasible, and that it is the widely acclaimed gold standard in the literature on adult populations.

PWA and AIx are not contingent upon any distance measurements but are even more dependent on the tonometric skill set of the operator. This technique needs to be developed and maintained to be able to hold the tonometer steady and with consistent pressure and to occlude the artery precisely from the top (and not from the side) without it rolling away. When PWA is performed on the radial artery, some have recommended practical strategies, such as bending the wrist over a towel to stabilize the arm and to expose the radial artery, holding the tonometer near the base for stability, and using fine adjustments to capture the waveform. The advent of software systems, such as the SphygmoCor device (AtCor Medical Inc.), that provide real-time feedback to the operator and can auto-capture results after a certain number of valid waveform acquisitions has occurred, have aided the operator in reliably collecting this measure. With appropriate training and practice, cfPWV and AIx measurements are highly reproducible, both within and between operators [29]. However, PWA and AIx have not been validated in adult populations to the same extent as cfPWV [24].

Oscillometrically derived PWV, such as brachial-ankle PWV (baPWV), addresses the above limitation of operator dependency. It has been shown that baPWV is systematically higher than cfPWV, as it measures both peripheral and central arterial segments, but there is a formula that can relate the two measures [24]. Oscillometric assessment of PWV using a pressure cuff has the advantages of being quick, convenient, and operator independent. Other

Fig. 3. PWV of a 7-year-old female compared to reference values for age and height. Adapted from Reusz et al. [25].

methods to measure PWV, such as MRI or echo-Doppler, are accurate and reliable but are time and labor intensive, expensive, and require the skills of a certified technician.

Whatever methodology is being utilized, it is important that operating procedures for the collection of studies are standardized and are reported in manuscripts. Choosing appropriate controls in pediatric research studies is important, particularly in conditions where growth retardation is prominent [30].

Conditions Associated with Arterial Stiffness

Primary Hypertension

cfPWV is a strong and independent predictor of cardiovascular events in adults with hypertension [13, 31]. A large study showed a graded increase in cfPWV from normotensive ($n = 531$) to prehypertensive ($n = 65$) to hypertensive ($n = 127$) youth aged 10–23 years (5.75 vs. 6.38 vs. 7.12 m/s, respectively), even after controlling for traditional cardiovascular risk factors in multivariate analysis ($p < 0.0001$) [32]. Similar results were observed for AIx

between normotensive, prehypertensive, and hypertensive groups (0.69 vs. 3.89 vs. 9.35%; $p < 0.0001$). Blood pressure stratification was determined for adolescents <18 years of age following recommendations from the 'Fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents' [33] and for those >18 years of age following the 'Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure' [34].

Obesity

In the United States, more than one third of children and adolescents are overweight (>85 th percentile) or obese (>95 th percentile), and 4–6% are severely obese (>99 th percentile) [35, 36]. Substantial attention has been given to the overall cardiovascular risk profile of obesity in youth, and several studies have shown a direct relationship of obesity with PWV in children [37]. An Australian study with 573 otherwise healthy, elementary school age children found that different measures of adiposity (BMI, waist circumference, and percentage of body fat) were independently correlated with cfPWV, even after controlling for demographics (age, sex) and blood pressure measurements (systolic blood pressure, mean arterial pressure, and heart rate) [38]. However, some studies have found no relationship, or even an inverse relationship, between obesity and indices of arterial stiffness, although differences in methodology may contribute to this finding [37, 39]. Dangardt et al. [40], in their study on 33 obese children and adolescents and 18 lean controls, interestingly found an increased carotid intima-media thickness (cIMT) and decreased radial-carotid PWV, hypothesizing that a general arterial vasodilation from hyperinsulinemia may be responsible for this functional difference.

Diabetes

Youth with type 1 and type 2 diabetes mellitus exhibit elevated PWV and AIx [41]. The SEARCH for Diabetes in Youth Study Group conducted a study with youth aged 10–23 years with type 1 ($n = 535$) versus type 2 diabetes ($n = 60$) and found that those with type 2 exhibited elevated cfPWV (6.4 ± 1.3 vs. 5.3 ± 0.8 m/s; $p < 0.01$) and AIx (6.4 ± 9.9 vs. $2.2 \pm 10.2\%$; $p < 0.01$) [42]. They also found that the association was largely mediated by increased blood pressure and central adiposity. In fact, obesity was associated with increased arterial stiffness independent of diabetes type in this cohort. In addition to cfPWV and AIx being elevated in otherwise healthy obese children as compared to lean controls, these measures were also elevated in obese adolescents with type 2 diabetes as compared to those without diabetes [43]. Similarly, arterial stiffness (cfPWV, AIx) was shown to be worse in obese participants enrolled in the above study with prediabetes (as determined by fasting glucose levels, glucose tolerance, or hemoglobin A_{1c}) than in obese participants without prediabetes, suggesting that arterial stiffening may occur early on in this disease process [44].

The SEARCH Study Group has also reported on some demographic differences in diabetes-related arterial stiffness. In youth with type 2 diabetes, African Americans were observed to have worse arterial stiffness than Caucasians [45]. The authors hypothesized that this difference could be related to the increased cardiovascular risk factor profile observed in African American adults as compared to Caucasian adults [46], but additional investigation is required to apply this to children and adolescents [45].

Chronic Kidney Disease

Several published studies have examined arterial stiffness in children with CKD. cfPWV and AIx are increased in children and adolescents with ESRD on dialysis versus healthy controls [30, 47]. One study found little improvement before and after the initiation of hemodialysis, suggesting that structural as opposed to functional changes are responsible for

increased arterial stiffness in this group [47]. Other pediatric studies have found lower cfPWV and AIx after renal transplantation, suggesting that transplantation can improve the arteriopathy associated with CKD [48–50]. While cfPWV tends to improve after renal transplantation, there is disagreement as to whether there is a difference between the cfPWV of patients with a functioning graft versus healthy controls [48, 49, 51, 52]. Hypertension is a risk factor for increased AIx in children with glomerulopathies, which was also higher compared to a healthy comparison group [53]. baPWV was increased in children with acute poststreptococcal glomerulonephritis, as compared to children with acute pyelonephritis and healthy controls [54]. Persistence of increased baPWV after acute poststreptococcal glomerulonephritis was seen in the setting of lasting renal damage [54]. Biomarkers of bone and mineral metabolism have also been shown to play a role in arterial stiffness in dialyzed children [52, 55, 56].

Very little data on arterial stiffness exist for children with mild CKD. One study, which focused on vitamin D deficiency, showed that for children across CKD staging, AIx increased with renal dysfunction [57]. Of the 43 participants aged 8–18 years with CKD (n = 4 with stage II; n = 7 with stage III; n = 12 with stage IV, and n = 20 with stage V), there was an inverse correlation between AIx and GFR (p = 0.004), 25-hydroxy vitamin D (p = 0.004), height (p = 0.004), and BMI (p = 0.005). There was also a significant difference between the AIx of the 43 participants with any stage of CKD and 19 control subjects (mean 13.44%, SE 2.41, vs. mean 6.36%, SE 2.32; p < 0.001).

Hypercholesterolemia

Children with primary or familial hypercholesterolemia exhibit increased PWV and AIx on Doppler echocardiography as compared to controls [58]. Additionally, a pilot study suggests that children with heterozygous familial hypercholesterolemia and severe periodontitis have higher cfPWV than their counterparts without periodontitis, although this difference was no longer significant after controlling for traditional cardiovascular risk factors [59]. The suggestion of increased PWV with periodontitis may be explained by a study showing that systemic inflammation, as measured by high-sensitivity C-reactive protein, is associated with elevated cfPWV and AIx in 78 adults with untreated hypertension [60].

Genetic Syndromes Involving Vasculopathy

There are a limited number of studies examining arterial stiffness in children with genetic syndromes involving vasculopathy. Higher AIx was observed in two studies with female Turner syndrome patients (mean age 17 years) as compared to controls [61, 62]. In contrast, cfPWV tended to be lower in Turner syndrome patients versus controls but was significantly higher after adjusting for body surface area [61, 62]. A recent study with the largest Williams syndrome cohort to date (77 patients, 36 of whom were pediatric) showed that cfPWV was significantly elevated in children with Williams syndrome, as compared to healthy controls (6.1 ± 1.0 vs. 5.1 ± 0.8 m/s; p < 0.0001) [63]. In regression analysis with the entire cohort (adults and children), cfPWV increased with age, but a faster rate of cfPWV increase with age was not observed in Williams syndrome patients versus controls. They also found that treatment with antihypertensive medication was a protective factor for increased cfPWV in Williams syndrome patients.

Interestingly, in two studies by the same group, PWV in children with neurofibromatosis type 1 was not elevated as compared to controls, and it was not associated with systolic blood pressure clinic measurements or 24-hour ambulatory blood pressure monitoring [64, 65]. No relevant articles were identified that focused on arterial stiffness in children with fibromuscular dysplasia or Alagille syndrome.

Solid Organ Transplantation

Coronary allograft vasculopathy is the leading cause of death and graft failure after heart transplantation, with rapid progression of atherosclerosis being a major concern [66]. In a study on 22 children with functioning grafts at least 6 months after heart transplantation, cfPWV was significantly increased as compared to a group of 95 controls (5.3 vs. 4.7 m/s; $p < 0.001$) in multivariate analysis [67]. There was also an indication of elevated cfPWV correlating with the age of the graft [PWV (in m/s) = $4.7 + (\text{age in years} \times 0.1)$; $p < 0.01$], although the sample size behooves cautious interpretation. A recent, small, exploratory study showed that PWV, as assessed by cardiac MRI, was elevated in 10 children after heart transplantation compared to reference values and was correlated with measures of coronary allograft vasculopathy (maximal and mean intimal thickness) [68].

Besides the studies examining arterial stiffness after pediatric heart and kidney transplantations, no studies focusing on other pediatric solid organ transplantations were identified.

Conclusions

Brachial artery blood pressure and pulse rate measurements are the clinical standard of care in the management of children. However, these give insufficient detail of the cardiovascular status in many children with chronic disease. The measurement of arterial stiffness in children is feasible and, under controlled conditions, can give accurate information about the underlying state of the arteries. This potentially adds valuable information about the functionality of the cardiovascular system in children with a variety of chronic diseases well beyond that of the brachial artery blood pressure.

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