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REVIEW

Pathophysiology and consequences of arterial stiffness in children with chronic kidney disease

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Abstract

Changes in arterial structure and function are seen early in the course of chronic kidney disease (CKD) and have been causally associated with cardiovascular (CV) morbidity. Numerous potential injuries encompassing both traditional and uremia-specific CV risk factors can induce structural arterial changes and accelerate arterial stiffening. When the buffering capacity of the normally elastic arteries is reduced, damage to vulnerable microcirculatory beds can occur. Moreover, the resultant increase to cardiac afterload contributes to the development of left ventricular hypertrophy and cardiac dysfunction. Adult studies have linked arterial stiffness with increased risk of mortality, CV events, cognitive decline, and CKD progression. Pulse wave velocity (PWV) is currently the gold standard of arterial stiffness assessment but its measurement in children is challenging due to technical difficulties and physiologic aspects related to growth and poor standardization between algorithms for calculating PWV. Nevertheless, studies in pediatric CKD have reported increased arterial stiffness in children with advanced CKD, on dialysis, and after kidney transplantation. Development of arterial stiffness in children with CKD is closely related to mineral-bone disease and hypertension, but other factors may also play a significant role. The clinical relevance of accelerated arterial stiffness in childhood on cardiovascular outcomes in adult life remains unclear, and prospective studies are needed. In this review we discuss mechanisms leading to arterial stiffness in CKD and its clinical implications, along with issues surrounding the technical aspects of arterial stiffness assessment in children.

Keywords Arterial stiffness · Children · Pediatric · Chronic kidney disease · Pulse wave velocity · Cardiovascular disease

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in children with stage 5 chronic kidney disease (CKD 5) [1]. The burden of CVD is particularly evident in young adults with CKD who have a nearly fivefold increased risk of ischemic heart disease (IHD) [2] and up to 55 and 20 years reduced life-expectancy on dialysis and after kidney transplantation, respectively [3]. Based on the significantly increased risk of premature CVD development, children with CKD 5 are classified as the highest pediatric CVD risk group [4].

Although overt CVD is rare in childhood, subclinical changes in the arterial tree are evident even in young children with CKD, and their prevalence increases with advancing CKD [5]. Arterial stiffness resulting from structural alterations associated with CKD represents an important independent axis of CKD-associated CV morbidity. In this review we discuss the pathophysiology and clinical relevance of CKD-associated arteriopathy and arterial stiffness, along with the technical aspects of its measurement in the pediatric population.

Arterial structure and function in healthy children

Arteries can be classified into large elastic arteries (aorta and its major branches) and smaller muscular (distributing) arteries found distal to aorta (e.g., radial and femoral arteries). All

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arteries have a similar triple-layered structure (tunica intima, media, and adventitia) but with a pronounced variation in the intrinsic composition of the arterial wall. Muscular arteries are smaller in diameter, and their medial layer is predominantly composed of vascular smooth muscle cell (VSMC) fibers. In contrast, the medial layer of large elastic arteries is mainly composed of multiple concentric layers of elastin fibers [6]. In healthy children, growth is associated with a gradual increase in the arterial wall diameter and total wall thickness. The latter increases predominantly due to the increase of intima-media layer and is directly related to increasing blood pressure (BP), age, and body dimensions and is gender-specific with higher arterial dimensions in boys [7].

The arterial system serves two principal functions: a conduit to deliver blood ejected by the left ventricle (LV) to the peripheral tissues and as vascular buffers that provide a "cushioning and dampening" function. Large elastic arteries behave similar to *Windkessel's*; these are elastic reservoirs, comparable with hydraulic pumps used by firefighters. The aorta and other central arteries store half of the stroke volume and accumulate approximately 10% of the energy generated by the LV during systole. The stored energy is required for effective arterial recoil during diastole which pushes out of the stored blood and thus ensures an uninterrupted blood flow reaching the microvasculature. The attenuation of the pulsatile nature of the blood flow generated by LV contraction also prevents damage that pressure oscillations could cause in the microcirculation [8].

Elastic properties of the large arteries are essential to ensure the buffering function of the arterial tree. Arteries are non-Hookean materials meaning they exhibit non-linear elasticity that depends on the BP [9]. Arterial elasticity is mainly determined by elastin fibers; however, at higher pressures, elasticity is lower and is predominantly maintained by collagen fibers [8]. If arterial elasticity is reduced (e.g., due to elastin fragmentation and loss), the arterial tree becomes stiffer. In physical terms, stiffness can be explained as resistance of an elastic object to strain (relative change in length) imposed by stress (force applied over an area) [10]. Increased arterial stiffness results in reduced arterial compliance and distensibility (change in arterial volume for a given change in pressure) and increased pulse wave velocity (PWV). The latter relationship is explained by the Moens-Korteweg equation ($PWV = \sqrt{Eh/2r\rho}$), according to which PWV is directly related to arterial elasticity (E) and wall thickness (h) and inversely to vessel radius (r) and blood density (ρ) [8].

Elastin has a very long half-life (up to 40 years), and its synthesis is most active during the perinatal period, declines thereafter, and becomes virtually negligible once adult dimensions are reached. [11]. This is reflected in children with intrauterine growth restriction who have stiffer arteries compared to age-matched controls [12, 13]. Although arterial stiffness in the pediatric population is usually viewed as pathological, healthy children demonstrate a gradual progressive increase in arterial stiffness with growth. This physiologic stiffening is accompanied by increasing arterial size and total arterial buffering capacity [14]. When measured by PWV, arterial stiffness is static in pre-school children and starts to rise gradually thereafter [12, 15–18]. The timepoint of PWV increase approximates the convergence of BP and PWV trajectories, suggesting that at a certain age the elasticity of the arterial wall is unable to further compensate for the increasing pulsatile stress to the arterial wall [16]. In adolescence, a divergence of arterial stiffness increase becomes apparent in girls and boys, with higher stiffness in the latter [12, 15–17, 19]. Finally, increasing height and body dimensions have a direct and independent effect on arterial stiffness [14, 17].

Risk factors for arterial pathology in children with CKD

Children with CKD are exposed to a wide spectrum of potential vascular injuries that can be broadly categorized into the 'traditional' (Framingham) CV risk factors and those that are CKD-specific (Fig. 1). The importance of individual traditional CV risk factors has been demonstrated in numerous studies showing premature vascular aging in children with diabetes, hypertension, obesity, and dyslipidemia [20–23]. More importantly, cohort studies such as the Bogalusa Heart Study [24] or the Young Finns Study [25] have shown the impact of childhood exposure to traditional CV risk factors on adult CV health. These landmark studies have linked development of premature atherosclerosis in adult life with childhood blood pressure, dyslipidemia, obesity, and smoking [24, 25] as well as cognitive dysfunction [26] and CKD in young adulthood [27]. It is hoped that results of ongoing collaborative initiatives, such as the International Childhood Cardiovascular Cohort (i3C), will further describe the effects of childhood risk exposure on CV events in adulthood [28].

Besides the traditional CV risk factors, uremia has a profound effect on vascular health. As discussed further in this article, several studies in children with CKD have shown that uremic CV risk factors, such as mineral-bone disease (CKD-MBD), hypertension and volume overload, inflammation, and oxidative stress, induce significant alterations in vascular structure and function. The prevalence and extent to which individual traditional or CKD-specific factors contribute to CVD development, however, depends on many different aspects such as primary kidney disease or degree of kidney function [29], but their interplay in the causal pathway of vascular damage in the pediatric CKD population is not always clear.

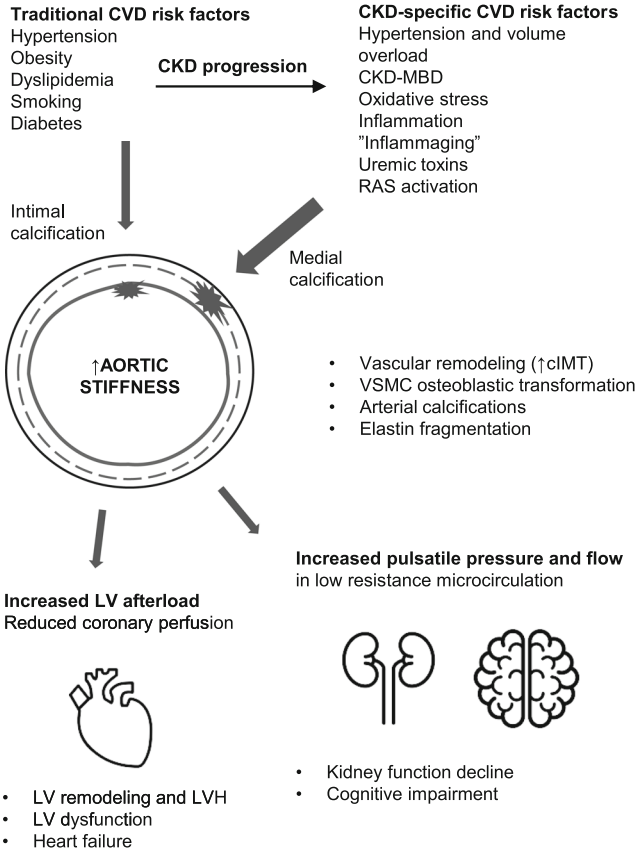

Fig. 1 Risk factors, mechanisms and consequences of arterial stiffness Abbreviations: *cIMT* carotid intima-media thickness, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *LV* left ventricle, *LVH* left ventricle hypertrophy, *MBD* mineral-bone disease, *VSMC* vascular smooth muscle cells

Mechanisms of arterial structural alterations in CKD

CKD is associated with significant structural changes in the arterial wall characterized by abnormal vascular remodeling and progressive arterial calcifications. The typical phenotype of uremic arteriopathy consists of arterial wall hypertrophy, reduced elastin content and arterial calcifications [30]. Vascular calcifications are considered to be the hallmark of CKD-associated arterial disease and may occur in either intimal or medial layers of the arterial wall. Intimal calcifications are typically observed in older patients when classical atherosclerotic plaques become evident [31]. In contrast, progressive calcification of the tunica media of large arteries, a distinct form of CKD-associated vasculopathy termed Monckeberg sclerosis, develops even in childhood [31, 32].

Medial calcification is seen even in young patients, and arteries from children with pre-dialysis or dialysis-dependent CKD reveal increased calcium load and hydroxyapatite deposition within the arterial wall [32]. In vitro studies examining arterial biopsies from patients with CKD have revealed that arterial calcification is a complex, active, and highly regulated process that develops and is exacerbated by dysregulated mineral metabolism, systemic inflammation, and oxidative stress [33, 34]. The calcification process involves the release of mineralizing lipid vesicles by vascular smooth muscle cells (VSMC) that contain abnormally reduced quantities of mineralization inhibitors (e.g., fetuin A, osteoprotegerin) [32, 35]. In addition, hyperphosphatemia induces apoptosis of VSMC and leads to deposition of mineralizing apoptotic bodies in arterial walls [32, 34].

Another distinct characteristic of arterial alterations in CKD is the osteoblastic transformation of VSMC induced by high serum phosphate levels [32] with an upregulation of bone-forming proteins such as alkaline phosphatase and the development of osteoblasts within the vessel wall [34]. Although phosphate is deemed to be the predominant vascular toxin in CKD, other components of CKD-MBD, such as deficiency of klotho and vitamin D, increased circulating fibroblast growth factor 23 (FGF23), and secondary hyperparathyroidism also plays a role in the calcification process [36]. In addition, iatrogenic factors, in particular the use of calcium-based phosphate binders and vitamin D analogs, may also contribute to the pro-calcific state [33].

Apart from the microstructural changes observed in arterial biopsies from children in CKD, clinically detectable arterial pathology has been reported even in young children. Measurement of the carotid intima-media thickness (cIMT) by high-resolution ultrasound of the carotid artery is a well-established marker of atherosclerotic burden. Increased cIMT has been observed in children with mild-to-severe CKD, on dialysis, and after kidney transplantation [5, 37–39]. In early CKD, dyslipidemia has been associated with increased cIMT [37], whereas in CKD stages 4–5 [5], and most markedly in patients on dialysis [39], CKD-specific risk factors are causally associated with vascular changes. Direct evidence of calcification, predominantly of the coronary arteries, has been shown on computed tomography in a smaller proportion of children with CKD 5 and on dialysis [39, 40].

Although dysregulated mineral homeostasis and CKD-MBD-related factors likely play a central role in arterial structural alterations observed in CKD, other factors, such as hypertension, oxidative stress, chronic inflammation and aging may also contribute to vascular damage. Arterial hypertension—a widely prevalent complication of CKD—increases pulsatile wall stress in major arteries and contributes to progressive elastin fragmentation [41]. Activated inflammatory cells in uremia produce cytokines that stimulate osteoblastic transformation of VSMC and release matrix metalloproteinases, cathepsins, and other proteolytic enzymes that induce elastin degradation and promote calcification [34]. Recently, accelerated vascular senescence, oxidative DNA damage, and inflammation, collectively termed "inflammaging," has been shown in children with CKD 5 and was closely correlated with vascular pathology [42].

Other factors, including endothelial dysfunction, renin-angiotensin-aldosterone system activation, uremic toxins and advanced glycation-end products may also affect vascular morphology to varying extents [34].

Arterial stiffness and functional consequences in CKD

Increased exposure to potential vascular injuries and aforementioned structural alterations may alter the function of large arteries and accelerate arterial stiffening in CKD, leading to several important clinical implications. Arterial stiffness is strongly related to aortic pulse pressure (PP) and is one of the major contributors to LV afterload (Fig. 2). According to the traditional view, the arterial system was seen as a two-element *Windkessel* where pressure-flow relationships are determined by arterial compliance and peripheral vascular resistance. These arterial properties, along with the cardiac output were also considered to be the determinants of PP [43, 44]. Later, a three-element *Windkessel* model was proposed that additionally incorporates aortic characteristic impedance, which is mainly determined by local aortic stiffness and aortic geometry [43, 45].

In addition, arterial stiffness contributes to the shape and magnitude of the aortic pressure waveform (PWf) by another indirect mechanism. According to the classical paradigm, the aortic PWf is a net result of forward and backward traveling waves. LV ejection creates a forward PWf that propagates distally towards peripheral tissues and multiple reflected waves are generated at points of impedance mismatch (e.g., arterial branching or diameter narrowing). The sum of these reflected waves creates a "net" reflected wave which returns to the proximal aorta. The timing when this reflected wave meets the forward-traveling waveform is critical and determined by PWV and left ventricular ejection time (heart rate, HR) (Fig. 2). At lower PWV and higher HR, the PW arrives in early diastole and allows for increased coronary perfusion during diastole. On the other hand, in case of a high PWV and low HR, the PW arrives in late systole, augmenting systolic BP (and PP) in the aorta [6, 8]. This simplified mechanism, however, has been debated, and a pressure augmentation model that incorporates aortic reservoir pressure and excess pressure related to wave propagations and reflections has been proposed [43].

Irrespective of the exact underlying mechanism, arterial stiffness represents an important mechanism that may damage major target organs: the heart, brain, and kidneys (Fig. 1). First, there is strong mechanistic evidence that increased arterial stiffness contributes to increased LV afterload which can result in LV remodeling and LV hypertrophy (LVH) [46]. In addition to the impaired ventricular-vascular coupling, increased arterial stiffness has also been linked to impaired coronary perfusion and myocardial hypoperfusion [47, 48]. The combined effect of these sequences can lead to diastolic and systolic LV dysfunction and development of clinically overt heart failure (HF). These mechanistic notions are supported by a meta-analysis of over 17,000 adults that linked increased PWV to higher risk of IHD, stroke and CVD events independent of the conventional risk factors, such as smoking, diabetes, hypertension, or kidney function [49].

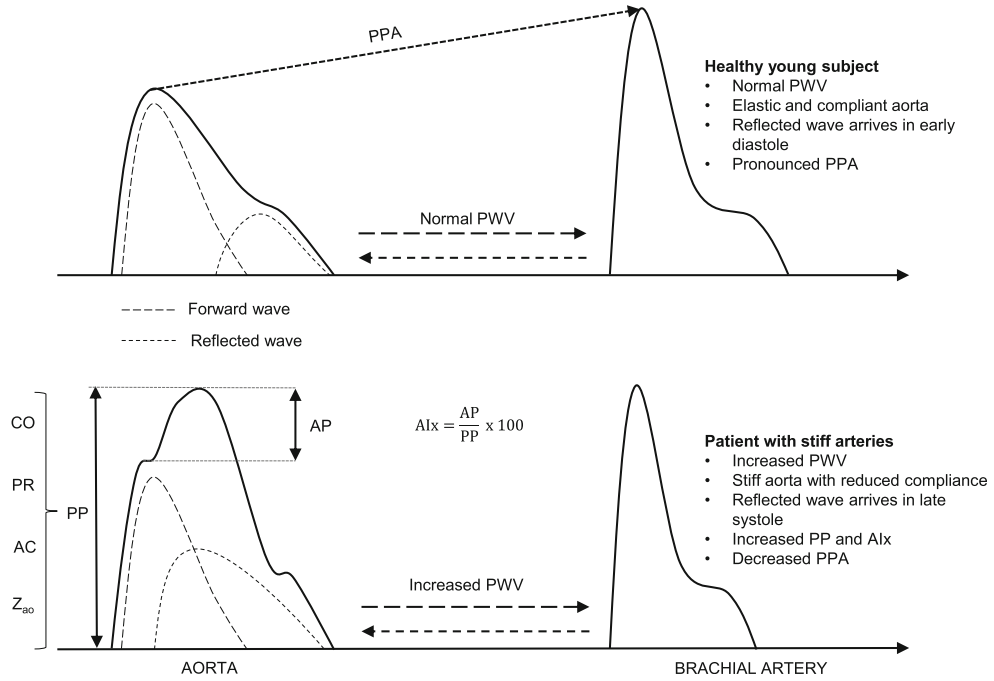

Fig. 2 Simplified schematic representation of pulse wave forms in healthy subjects and patients with increased arterial stiffness. Abbreviations: *AC* arterial compliance, *AIx* augmentation index, *AP* augmented pressure, *CO* cardiac output, *PP* pulse pressure, *PPA* pulse pressure amplification, *PR* peripheral resistance, *PWV* pulse wave velocity, Z_{ao} characteristic aortic impedance

A second important consequence of abnormal arterial stiffening is the reduced "cushioning" capacity of the stiff arterial tree which results in the transfer of pulsatile blood flow generated by intermittent LV contractions into the microvasculature. Organs such as the brain and kidneys that are dependent on continuous perfusion and have a widely spread low-resistance microvascular network are particularly susceptible to damage caused by the exaggerated pulsatile pressure and flow [50]. Clinical studies in adults without kidney disease have reported the adverse effects of increased arterial stiffness on cognition and kidney function [51, 52].

Measuring arterial stiffness in children with CKD

Measuring early changes in the arterial system is important to quantify the presence and severity of subclinical arterial disease and to evaluate the remote risk of overt CVD development. Measurements of structural changes are important to understand the degree of premature atherosclerosis or arterial calcifications but are not directly representative of arterial stiffness; patients with CKD show moderate correlation between cIMT and parameters of arterial stiffness, but these may represent differential arterial response to various vascular injuries [5, 53, 54]. While cIMT reflects the degree of premature atherosclerosis in children, arterial stiffness directly represents a functional risk factor of CKD arteriopathy and may have superior predictive value [53, 55].

Several different parameters may be used to evaluate arterial stiffness in children. In general, they can be categorized into (i) elasticity parameters (distensibility, Young's elastic modulus, β-stiffness index), (ii) PWV, and (iii) pulse wave analysis (PWA)-derived parameters (central BP, augmentation index (AIx)). The mechanistic and technical details of these approaches, along with their pros and cons, are outside the scope of this review and have been discussed elsewhere [56–58]. Of note, PWA-based parameters that are frequently used as markers of arterial stiffness are derived from other hemodynamic measures and are not directly representative of stiffness [57]. Overall, based on its clinical applicability, strong physiological basis and associations with clinical outcomes, carotid-femoral PWV (cfPWV) is currently recommended as the "gold standard" for arterial stiffness assessment [59–62]. PWV is also recognized as a proxy of target organ damage in adult and pediatric hypertension guidelines [63–65].

Several types of devices for noninvasive assessment of cfPWV are available. Noninvasive estimation of cfPWV typically relies on the calculation of the time (transit time, TT) that a pulse waveform takes to travel a distance between two measurement points in the carotid and femoral arteries (Fig. 3). This involves obtaining PWf in the respective arteries by means of applanation tonometry, mechanotransducers, ultrasound or oscillometry, and over-the-skin measurements of the travel distance. The TT between the proximal and distal recording sites is then estimated by calculating the time delay between the two systolic upstrokes ("foot-to-foot" method) of PWf (Fig. 3). Some devices, however, employ techniques that

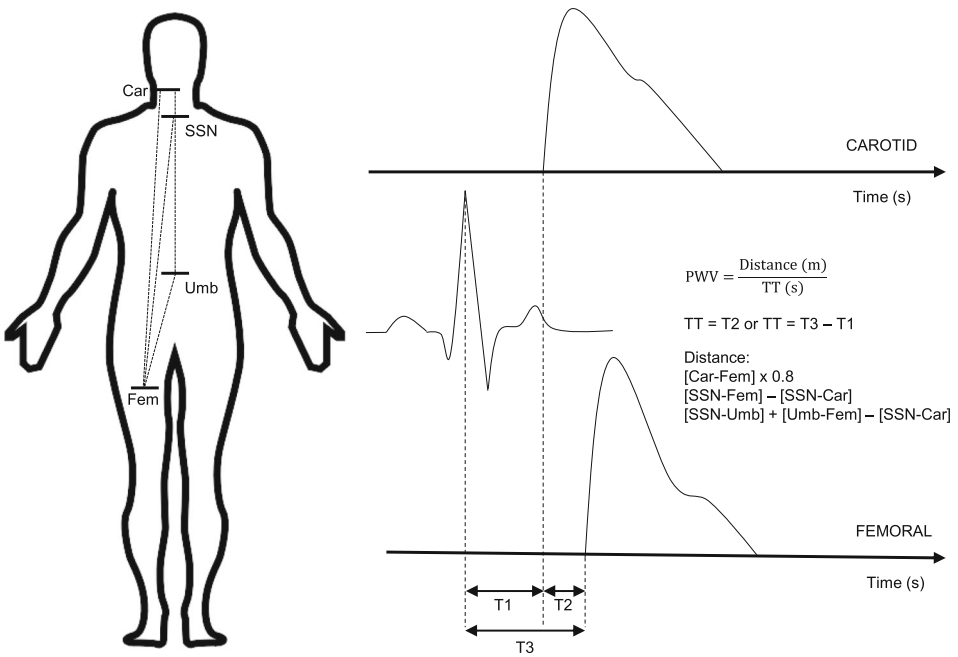

Fig. 3 Examples of travel distance and transit time estimations for cfPWV calculation. Abbreviations: *Car* carotid artery, *Fem* femoral artery, *PWV* pulse wave velocity, *SSN* suprasternal notch, *TT* transit time, *T* time, *Umb* umbilicus

involve single point measurements and statistical algorithms (transfer functions) to estimate presumed PWV [58]. Among the noninvasive techniques, magnetic resonance imaging (MRI) provides most accurate TT and distance measurements, but its use is limited in routine pediatric practice [57]. Common devices and techniques for PWV assessment are summarized in Table 1.

Several factors must be considered when choosing the appropriate device for cfPWV measurement in children. Feasibility of measurements is an important consideration and depends on the age and cognitive function of the child. Techniques involving tonometric readings or suprasystolic-inflated brachial cuffs are time-consuming and may be uncomfortable for younger children leading to measurement failure [71, 76]. Tonometric recordings also require trained operators and strict adherence to quality criteria that may not be possible, making this technique observer-dependent and fraught with bias, particularly in longitudinal follow-up studies [77]. Oscillometric or other newer devices, such as Mobil-o-Graph or the pOpmetre [58], may be more attractive alternatives but may provide less reliable results due to the indirect nature of measurements. Device validation is an important aspect and according to the guidelines devices for use in children should be validated in children [61, 78]. Several devices have undergone validation in the pediatric population against the noninvasive gold standard (SphygmoCor) (Table 1) [67, 68, 71–73]. Of those, tonometric (SphygmoCor and PulsePen) and oscillometric (Vicorder) devices have gained most popularity in the pediatric CKD population.

The inherent differences between the devices for noninvasive cfPWV measurements preclude direct inter-device comparisons of the results. This is partly due to technical differences (e.g., devices using TT and distance measurements vs. devices using transfer function) but also due to other aspects of the cfPWV measurement procedure, including travel distance measurements. In adults, 80% of the direct measurement between the carotid and femoral measuring sites or subtraction of the carotid-suprasternal notch (SSN) distance from SSN-femoral distance have shown best anatomic and cfPWV

Table 1 Techniques and devices for cfPWV measurements and available data from pediatric studies

Device	Method	Pathway[a]	Clinical usability[b]	Validation in children	Device-specific pediatric reference values
SphygmoCor (Atcor Medical)	Applanation tonometry Single sensor ECG-gating required	A, B	+++	Gold standard	Yes [17, 66] Age: 6–20
PulsePen (DiaTecne)	Applanation tonometry Single sensor ECG-gating required	A	+++	Yes [67]	Yes [17] Age: 6–20 years
SphygmoCor Xcel (Atcor Medical)	Carotid tonometry Femoral cuff, simultaneous	A	+	Yes [68]	No
PulsePen ETT (DiaTecne)	Applanation tonometry Two sensors, simultaneous	A	–	No	No
Complior (Alam Medical)	Piezoelectric mechanotransducers Two sensors, simultaneous	C	+++	No	Yes [69] Age: 5–17 years
Aortic (Exxer)	Piezoelectric mechanotransducers Two sensors, simultaneous	D	+	No	No
Arteriograph (TensioMed)	Oscillometric Single brachial cuff	E	++	No	Yes [16, 70] Age: 3–22 years
Mobil-o-Graph (IEM)	Oscillometric Single brachial cuff	–	++	No	Yes [15] Age: 8–22 years
Vicorder (Skidmore Medical)	Oscillometric Two cuffs (carotid and femoral), simultaneous	A, B, F	++	Yes [67, 71, 72]	Yes [12, 19] Age: 5–19 years
pOpmetre (Axelife SAS)	Two photodiode sensors (fingers and toes), simultaneous	Height-derived	++	Yes [73]	No
Doppler ultrasound	Doppler probes ECG gating might be required	Height-derived	++	–	Yes [74] Age: 0–20 years
MRI	MRI	Direct estimation	+	–	Yes [75] Age: 2–28 years

cfPWV carotid-femoral pulse wave velocity, *ECG* electrocardiography, *MRI* magnetic resonance imaging

a) A: [Femoral-SSN] – [SSN-Carotid]; B: [Carotid-Femoral] × 0.8; C: [Carotid-Femoral]; D: [Carotid-Femoral] – [Carotid-SSN]; E: [SSN-Symphysis]; F: [SSN-Umbilicus] + [Umbilicus-Femoral] – [SSN-Carotid] (SSN = suprasternal notch)

b) According to the judgment of adult studies by Milan et al. [58]

measurement accuracy [61]. A recent study in children has indicated that the subtracted distance estimation is more reliable when compared with 80% of the direct measurement which overestimated the MRI-determined aortic pathway by up to 10% [79]. In children, the agreement of the oscillometric Vicorder device with SpygmoCor was strongly influenced by pathway calculation for the Vicorder measurements (Fig. 3). Subtracted distance and distance calculated via umbilicus, but not the direct pathway measurement, showed excellent agreement between the two devices in several validation studies [67, 71, 72].

All of these considerations must be taken into account when choosing the reference values for cfPWV in children. Selected reference data has to be device-specific and similar TT distance calculation (if required) should be employed. Comparison of available reference data showed differences in the established reference values using different devices, with a significant difference between measurements obtained with the Arteriograph compared with other devices [12, 15]. Moreover, height is an important and independent determinant of cfPWV in children; therefore, the choice of height or age-standardized reference values is important [12, 15, 17–19]. Age-specific reference values can underestimate PWV in small-for-age children [12]. This may be of particular importance for accurate stiffness assessment in the pediatric CKD population, wherein short stature is prevalent [80, 81]. The availability of device-specific reference values for children is summarized in Table 1 [12, 16, 17, 19, 66, 69, 70, 74, 75].

Arterial stiffness in CKD: Lessons from adult studies

Arterial stiffness has been extensively studied in adults with CKD, and landmark studies, such as the Chronic Renal Insufficiency Cohort (CRIC) study, have clearly established a link between advancing CKD and increasing arterial stiffness [82]. In over 2500 adults from the CRIC study, cfPWV increased by 0.23 m/s per each 10 ml/min/1.73 m^2 decrease in estimated glomerular filtration rate (eGFR) [82]. In CKD 5 patients the dialysis modality has an important effect on arterial stiffness, with accelerated stiffening on hemodialysis (HD) as compared with peritoneal dialysis (PD). The differences are mainly related to residual kidney function and higher volume overload in patients on HD who also demonstrate cyclical pre-/post-HD session variability in cfPWV [83]. The benefits of kidney transplantation on arterial stiffness and cfPWV remain unclear and may be influenced by the change in risk factor profile, but patients with a kidney transplant have a higher cfPWV compared with the healthy adult population [84].

Importantly, arterial stiffness has been correlated with hard outcomes in adults with CKD. As in the general adult population, increased cfPWV was attributed to higher risk of eGFR decline in adults with CKD [85]. Similarly, increased cfPWV was related to cognitive impairment or development of dementia [82, 86]. Studies of adults with advanced CKD and on HD also revealed independent associations of PWV with development of fatal and non-fatal CV events, incident hospitalized heart failure and all-cause mortality [55, 82, 85]. Importantly, the predictive value of cfPWV appears to outweigh that of conventional blood pressure measurements [82]. The associations of increased cfPWV with adverse outcomes, including all-cause mortality and CV events, are not ameliorated by kidney transplantation and associations with graft dysfunction have also been reported [84].

Clinical studies in children with CKD

Data about cfPWV in the pediatric CKD population remains relatively scarce and largely comes from small case-control studies (summarized in Supplementary Table 1). In contrast to the adult population, studies in children with CKD do not reveal direct associations between eGFR and cfPWV [5, 87–90]. Available evidence suggests that in earlier CKD stages, when uremia-related risk factors are less pronounced, arterial elastic properties in children remain relatively unchanged. Two large studies involving children with mild-to-moderate CKD reported similar cfPWV compared with healthy children [87, 91]. In fact, the determinants of cfPWV in children with early CKD stages were age, BP, and black race [87]—the same as reported in healthy children [12, 15–19]. Studies of children with more advanced CKD, however, have reported increased cfPWV, especially in children on dialysis [5, 92–97]. In a large cohort of European children with advanced CKD, increased cfPWV was reported in 20% of the study population [5]. Interestingly, increased cIMT was observed in over 40% of participants in this study and showed only a moderate correlation with cfPWV, implying that structural changes in the arteries precede the development of vascular stiffness.

In contrast to the findings in those with early kidney dysfunction, the determinants of cfPWV in children with advanced CKD and on dialysis are in line with the findings of arterial biopsy studies. Several studies have reported strong associations of cfPWV with markers of CKD-MBD, including serum fetuin A or fetuin A/Ca × P ratio, parathyroid hormone (PTH), bone alkaline phosphatase, and lower levels of vitamin D [5, 39, 94, 98, 99]. In addition, a dose-dependent effect of treatment with active vitamin D on increased cfPWV was observed in children on dialysis and after kidney transplantation [39, 81, 98]. Furthermore, the gut-derived uremic toxin indoxyl sulfate, but not p-cresyl sulfate, was

independently predictive of cfPWV increase over 12 months in children with CKD [100]. Whether this represents an effect of altered gut microbiota remains unclear, but microbiota composition was not correlated with cfPWV in children with mild CKD [89].

BP appears to be the only factor independently and strongly associated with cfPWV in children across all CKD stages [5, 87, 90, 96, 101, 102]. Higher PWV has been reported in patients with different ABPM profile abnormalities [90], and a recent study reported night-time and sustained hypertension to be independent predictors of PWV in children with CKD. Interestingly, lower PWV was observed in patients with a normal ABPM profile taking antihypertensive medications compared with untreated patients [101]. Whether this is related to the possible beneficial effect of frequently prescribed RAS inhibitors on arterial stiffness in pediatric CKD is intriguing [41]. Studies in pediatric CKD did not demonstrate direct associations with body mass index (BMI) and increased arterial stiffness [5, 87]. However, recently both underweight and overweight children with CKD and on PD have been reported to be at increased risk of higher PWV. In addition, lower adipose tissue mass was independently associated with lower odds of increased PWV [93]. The U-shaped relationship of PWV with BMI may reflect the importance of the malnutrition-inflammation-arteriopathy axis [103] and resemble the associations between cholesterol and mortality in adults with CKD [104].

Similar to BMI, direct independent associations of PWV with dyslipidemia were not identified in children with pre-dialysis CKD [5, 87]. Instead, current evidence suggests that the effects of traditional CV risk factors cannot be directly transferred to the pediatric CKD population and may be significantly confounded by the uremic milieu. For instance, it has been shown that qualitative changes in HDL, but not quantitative lipid abnormalities, may induce vascular injury and associate with arterial stiffness in pediatric CKD. Nitric oxide (NO) release induced by high-density lipoprotein (HDL) cholesterol, but not HDL levels, was significantly correlated with cfPWV [105]. Two other studies also reported correlations between markers of the NO pathway and cfPWV in children with pre-dialysis CKD [90, 106]. The relationship between endothelial dysfunction and cfPWV was further demonstrated by a study which showed an independent association between cfPWV and circulating endothelial microparticles [102].

The effects of kidney replacement therapies (KRT) on arterial stiffness in the pediatric population have not been studied extensively. Increased cfPWV has been reported in children on PD, HD, and after kidney transplantation with the highest values in children on HD [80, 81, 92–95, 98, 102, 107]. Although patients on HD demonstrate highest arterial stiffness, a recent study investigating the effects of hemodiafiltration (HDF) on heart and height (3H Study) reported a significant decrease of cfPWV over time in patients on HD and HDF. In the 3H Study, HDF attenuated progression of cIMT when compared with HD, but the annualized change of cfPWV did not differ between patients on conventional HD and HDF. The determinants of cfPWV in this large multicenter cohort were interdialytic weight gain, BP, lower hemoglobin, and higher PTH [108].

A longitudinal study of 15 children who underwent kidney transplantation after previous HD did not reveal a significant change in cfPWV within 6 months after the transplantation [109]. However, a study investigating the effects of pre-emptive KRT initiation in children with CKD 5 showed that pre-emptive kidney transplantation was associated with a decrease of cfPWV compared with the initiation of dialysis [110]. Irrespective of the dynamic changes, arterial stiffness appears to remain increased in the pediatric kidney transplant population [97, 98, 109] and may relate to a novel spectrum of risk factors. Studies in children, however, did not report a significant effect of calcineurin inhibitors or obesity on arterial stiffness [109, 111]. Instead, cumulative calcitriol dose, dialysis for more than 1 year, and impaired kidney function have been linked to cfPWV augmentation [81, 98]. Of note, patients with a decrease in cfPWV after kidney transplantation had better graft function [109].

Although available evidence suggests that arterial stiffness is prevalent in children with advanced CKD, studies of its functional consequences and long-term effects on CVD outcomes in adult life are still lacking. PWV was not associated with LVMI in a small study of children on HD but correlated in children with autosomal dominant polycystic kidney disease [107, 112]. In contrast, in the adult CKD population, increased PWV was associated with structural remodeling of the left ventricle and left atrium, myocardial fibrosis and LV twist mechanics [113–115]. Whether other CKD-related risk factors of LV remodeling surpass the effect of arterial stiffness in children requires further studies. One of the explanations for these differences, however, could be age dependency of the hemodynamic effects of PWV on LV afterload. In a study that included adults of different age, increased PWV in younger patients may be a consequence of increasing velocity of myocardial shortening and may represent increased intraventricular PWV [116].

Conclusions and implications for future research

Increased arterial stiffness is an important risk factor that correlates with arterial disease and has been linked to adverse cardiac, kidney, and cognitive outcomes in adult populations. PWV is a validated and feasible technique that allows for noninvasive evaluation of arterial stiffness in children but careful considerations must be made in choosing the

appropriate techniques and reference data. Current evidence indicates accelerated arterial stiffening in children with CKD, but the exact mechanisms and consequences remain to be clarified. Prospective longitudinal studies with a particular focus on the association with CV and kidney outcomes in early CKD are needed to describe the natural course and long-term effects of arterial stiffening in childhood. Finally, studies investigating interventions targeting major risk factors of arterial stiffness—CKD-MBD, arterial hypertension, and inflammation—should consider including cfPWV as a surrogate marker of arterial health.

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Compliance with ethical standards

Conflicts of interest/competing interests The authors declare that they have no conflict of interest.

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