Early Vascular Ageing and New Approaches to Paediatric Hypertension

João Ferreira Simões,[1] Rute Baeta Baptista[1,2]

1. Unidade de Nefrologia Pediátrica, Hospital D. Estefânia, Unidade Local de Saúde São José, Lisboa, Portugal. Centro Clínico Académico de Lisboa, Lisboa, Portugal.
2. NOVA Medical School / Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal.

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death and loss of disability-adjusted life years worldwide. Identifying individuals at high risk for CVD early in life remains a major public health priority. The concept of vascular age has improved traditional risk stratification for CVD. Children with hypertension show signs of premature vascular ageing, suggesting their vascular age is four to five years older than that of their normotensive peers. This phenotype continues in adulthood, probably reflecting haemodynamic stress and cardiometabolic/inflammatory-driven changes in the vascular system as part of an accelerated biological maturation profile. Increased carotid-femoral pulse wave velocity, the gold standard measurement of arterial stiffness and premature vascular ageing, is an age-independent predictor of CVD-associated and all-cause mortality. Halting or reversing the markers of vascular ageing is emerging as a potential strategy to tailor the treatment of hypertension in young populations. A deeper understanding of why some individuals are highly susceptible to CVD, while others seem to be relatively protected throughout life, may help further individualise approaches to the prevention, follow-up, and treatment of paediatric hypertension.

Keywords:

Arterial stiffness, cardiovascular disease, child, early vascular ageing, hypertension, pulse wave velocity.

Abbreviations and Acronyms:

ACEi: Angiotensin-converting enzyme inhibitors
cfPWV: Carotid-femoral pulse wave velocity
cIMT: Carotid intima-media thickness
CKD: Chronic kidney disease
CVD: Cardiovascular disease
EVA: Early vascular ageing
FMD: Flow-mediated dilation
HVA: Healthy vascular ageing
PWV: Pulse wave velocity
SBP: Systolic blood pressure
SUPERNOVA: Supernormal vascular ageing

Corresponding author:
Email: joao.f.ferreira.simoes@gmail.com
Received: 4/2/2024 Accepted: 18/2/2024

INTRODUCTION

Vascular health has long attracted medical attention due to its prognostic value, from ancient semiological descriptions of arterial pulses to autopsy studies associating arterial calcification with ageing and premature death[1,2]. More recently, in 2008, early vascular ageing (EVA) emerged as an integrative concept of cardiovascular risk, reflecting the cumulative effects of all cardiovascular risk factors in vascular system structure and function. More importantly, studies have shown EVA to predict cardiovascular and all-cause mortality[3,4]. The individual trajectory of vascular ageing seems to depend on genetic background, starting as early as childhood or even foetal life, later modified by environmental factors. While hypertension is the strongest modifiable risk factor for EVA, non-haemodynamic cardiovascular disease (CVD) risk factors such as visceral adiposity, impaired glucose metabolism, hypercholesterolemia, smoking, and chronic inflammation also seem to play a role[5]. As significant progress has been made to develop non-invasive methods to assess vascular health, moving these concepts from bench to clinical practice is closer to becoming a more universal reality, further improving CVD risk stratification and target organ damage assessment[6]. Studying the mechanisms underlying interindividual heterogeneity in the rate of vascular ageing may also help identify new targets to prevent and treat CVD [3,7].

ARTERIAL PHYSIOLOGY

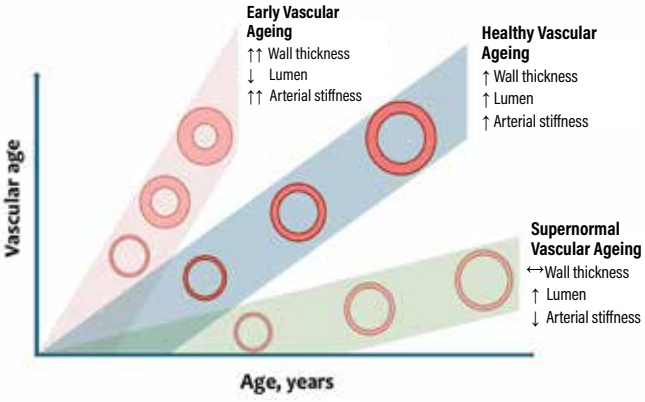
Arteries are the higher-pressure portion of the circulatory system. Large, central, conducting, or elastic arteries are the ones more proximal to the heart with an

elastin-rich media layer. Medium-sized, distributing or muscular arteries are named anatomically (for example, brachial artery, radial artery, and femoral artery), poorer in elastin, richer in collagen and have smooth muscle cells. Healthy elastic arteries play a key role in converting pulsatile flow originating from the left ventricle into a seamless and continuous flow of blood at microcirculation level to steadily supply tissues with nutrients and oxygen across the entire cardiac cycle (Windkessel effect)[8]. The aorta is the dominant elastic artery. Following ventricular ejection during systole, the elasticity of the aorta allows it to act as a hydraulic reservoir, decreasing systolic blood pressure (SBP). By using energy stored during systole, the aorta recoils during diastole, increasing diastolic blood pressure and coronary perfusion. Combined, these effects on systolic and diastolic blood pressure reduce pulse pressure and excessive pulsatility throughout the vascular system, maintaining continuous blood flow to the organs. Additionally, healthy elastic arteries promote a more efficient ventricular-vascular coupling by reducing left ventricular afterload[3,8,9].

THE CONCEPT OF EARLY VASCULAR AGEING (EVA)

Arterial age can be evaluated based on the assessment of i) arterial structure, by measuring carotid intima-media thickness (cIMT); ii) arterial elasticity, by determining arterial pulse wave velocity (PWV); and iii) endothelial function, by quantification of flow-mediated dilation (FMD) of the brachial artery. With age, cIMT and PWV increase while FMD decreases[5]. Microcirculation also changes with age, as shown by the narrowing and loss of arterioles in the retina[10]. Interestingly, the rate at which these changes occur is strikingly variable and seems to explain, at least partially, the individual differences in CVD risk within comparable age groups. Studying this variability has led to the concept of extremes in vascular ageing phenotypes. Thus, early vascular ageing (EVA) and supernormal vascular ageing (SUPERNOVA) represent the two opposite ends of the spectrum, while healthy vascular ageing (HVA) comprises the physiological or normal range of intermediate phenotypic variability (Figure I)[4]. Over time, large arteries become stiffer due to a decrease in elastin, in parallel with an increase in collagen cross-linking, mucopolysaccharide matrix deposition, and calcification. At a molecular level, shear stress, reactive oxygen species, chronic low-grade inflammation, telomere attrition, epigenetic alterations, and an imbalance favouring vasoconstrictors against vasodilator mediators seem to drive structural and functional changes[6]. Normal vascular ageing implies some degree of hypertrophic remodelling, or medial hypertrophy, leading to increased arterial wall thickness. Meanwhile, central arteries undergo an eccentric remodelling as they lose elastin, which increases their lumen. As a result, in HVA, the media-to-lumen ratio remains approximately the same. In contrast, individuals with EVA show patterns of precocious and faster

Figure I. Graphic representation of vascular ageing processes and phenotypes.



Graphic representation of vascular ageing processes and phenotypes. Adapted from "Age and Vascular Aging: An Unexplored Frontier" from González, LM. *et al.* (2023).

vascular ageing processes with impaired damage repair mechanisms[11], which result in excessive wall thickness and decreased arterial lumen. This leads to a media-to-lumen ratio and degree of arterial stiffness that are higher than expected for their chronological age. Conversely, in the SUPERNOVA phenotype, wall thickness remains stable with increasing vascular lumen, and arterial stiffening seems to be absent, which results in increased distensibility[11]. In other words, while HVA is characterised by a similar vascular age to chronological age, EVA is defined by older arteries and SUPERNOVA is defined by younger arteries than expected for the chronological age. This categorisation is based on the extremes of statistical distribution for quantitative markers of vascular age in a population (PWV). Although the most frequent values in a population do not necessarily represent the healthiest range, the concepts of EVA and SUPERNOVA have been validated as predictors of the rate of cardiovascular events among adults, according to the Malmö Diet and the Cancer Study cohort. Vascular phenotype categories were based on the 10th and 90th percentiles of the difference between arterial age and chronological age. Vascular age in the SUPERNOVA group was about six years below their chronological age, and it was associated with an age- and sex-adjusted 40% lower rate of cardiovascular events compared to individuals with HVA[9].

MARKERS OF EARLY VASCULAR AGEING IN PAEDIATRIC HYPERTENSION

Increased Carotid Artery Intima-media Thickness

Increased carotid artery intima-media thickness (cIMT) is a well-established predictor of coronary and cerebrovascular events in adults[12]. In children with newly diagnosed hypertension, cIMT was higher than in their body mass index-matched counterparts, and closely associated with various ambulatory blood pressure

monitoring parameters, including daytime SBP load and daytime SBP index[13]. Similarly, in a paediatric hypertension clinic, 28% of patients had increased cIMT, which was significantly associated with left ventricular hypertrophy, suggesting a common pathway for maladaptive arterial and cardiac remodelling under increased pressure stress[13,14]. Furthermore, abnormal cIMT in childhood seems to persist into adulthood. The International Childhood Cardiovascular Cohorts (i3C) Consortium showed that childhood SBP, mean arterial pressure, and pulse pressure predict cIMT in young adults 25 years later, and a meta-analysis of 19 studies also highlighted an association between SBP in childhood and the subsequent development of increased cIMT in adulthood[15,16]. Vascular ultrasound is thus emerging as a valuable tool to assess early changes in vascular health among young people with hypertension and other cardiovascular risk factors.

Increased Pulse Wave Velocity

Left ventricular ejection initiates a pulse wave that spreads throughout the arterial system. Propagation velocity is influenced by elastic and geometric properties of the arterial wall. Higher arterial stiffness (lower distensibility) leads to higher PWV. The carotid-femoral PWV (cfPWV), which reflects the speed at which the pulse wave travels through the aorta, or central PWV, is the gold standard for assessing arterial stiffening, being a strong predictor of future cardiovascular events and all-cause mortality in adults. Among adolescents with hypertension, PWV was noted to be higher compared to normotensive controls[17]. In a cross-sectional analysis of healthy adolescents, higher blood pressure, higher BMI, male sex, and higher total homocysteine levels were independently associated with arterial stiffness[18]. Similar associations were found between higher blood pressure assessed using 24-hour ambulatory blood pressure monitoring and increased cfPWV in children and young people followed up in hypertension clinics, where 24-hour SBP variability and daytime SBP variability were the independent determinants of increased PWV[19]. In the same population, PWV has also shown to be higher in obese children with hypertension, regardless of their weight. Increased cIMT and PWV are present even in children with high blood pressure before the onset of overt hypertension, highlighting the potential importance of studying these markers of vascular health as early signs of target organ damage[20,21]. High blood pressure in childhood persists into adulthood and predicts increased cIMT, raised PWV, and higher left ventricular mass during the fourth and fifth decades of life. A meta-analysis of longitudinal studies found an association between these markers of vascular ageing and increased cardiovascular morbidity and mortality[16]. Arterial tonometry is a non-invasive and relatively inexpensive method to reliably measure PWV. Improving instrumental methods to minimise reliance on skilled personnel to perform arterial stiffness measurements is crucial to expanding its use in clinical settings[22].

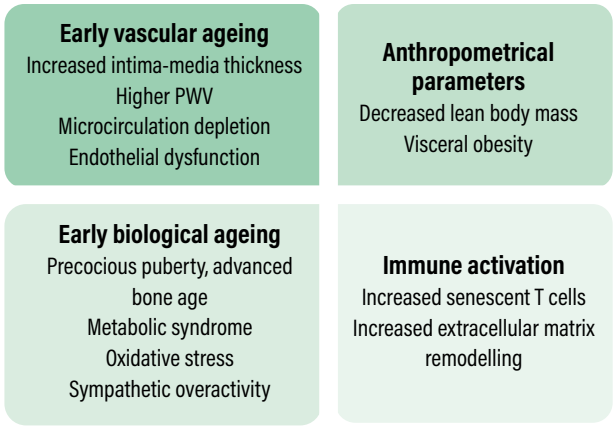
Endothelial Dysfunction

One the best studied non-invasive quantitative markers of endothelial function is ultrasonographic assessment of brachial artery flow-mediated dilatation (FMD) in response to hyperaemia after occlusion with an inflated cuff, a physiological phenomenon that mainly depends on a normally functioning endothelium. The higher the FMD, the healthier the endothelium[23]. Reduced FMD has been linked to increased cIMT and left ventricular mass in adults, even in prehypertensive populations[24]. Abnormal FMD has also been reported among paediatric patients with obesity, diabetes and hypertension[25]. In a 10-year longitudinal study, adolescents with low-normal FMD showed a significantly greater increase in left ventricular mass, cIMT, and SBP than their peers with normal baseline FMD, highlighting the interaction between blood pressure, endothelial function, and cardiac remodelling[26]. Similarly, the Framingham Offspring Study's prospective analysis found an association between early changes in endothelial function and arterial distensibility with the development of hypertension, suggesting that these arterial changes may even precede hypertension and play a role in its development[27]. Age- and sex-specific percentiles for brachial artery FMD in the healthy population have recently become available and may help move endothelial function assessment from bench to bedside[23].

EARLY VASCULAR AGEING AS PART OF ACCELERATED BIOLOGICAL MATURATION

Multiple factors contribute to EVA in children and adolescents (Figure II). This phenotype is more common among individuals with hypertension and those with physical and laboratory characteristics previously associated with metabolic syndrome, such as increased waist circumference and impaired glucose metabolism. Chronic inflammation and oxidative stress are non-haemodynamic factors also known to contribute to EVA[5]. Growth spurts and the underlying metabolic changes during childhood and adolescence are associated with an increase in blood pressure, as well as structural and functional alterations in arterial vessels[28]. Key factors contributing to high blood pressure in children are increased body mass index, high waist circumference and male sex[29,30]. Remarkably, one recent study linking the origin of primary hypertension to early life programming and modulation later in life highlighted prematurity and low birth weight as the most relevant contributors[31]. The prevalence of primary hypertension rises markedly after puberty. Vascular remodelling also tends to accelerate over puberty, possibly influenced by the metabolic alterations associated with growth, contributing to increase blood pressure[32]. The increase in blood pressure appears to be the main driver for the arterial changes leading to stiffening[27]. This vicious circle suggests both primary hypertension and EVA may be signs of accelerated biological maturation[33].

Figure II. Features of early vascular ageing.



Schematic representation of factors contributing to early vascular ageing, divided into four main groups. Adapted from "Origins of Primary Hypertension in Children: Early Vascular or Biological Aging?" from Litwin, M. and Feber, J. (2020).

VASCULAR AGEING AND NEW APPROACHES TO PAEDIATRIC HYPERTENSION

Vascular Ageing Reversibility

Signs of maladaptive vascular remodelling among children and adolescents with hypertension suggest their arteries are four to five years biologically older than those of their normotensive peers, adjusting for age and sex[34,35]. These changes persist into adulthood and predict CVD-associated morbidity and mortality later in life. Indeed, prospective data suggests children and adolescents with hypertension who later normalise their blood pressure do not develop increased cIMT and PWV in their fourth decade of life[36]. Even during childhood, children with signs of EVA show improvement after adequate intervention. Prepubertal obese children under dietary intervention and physical exercise showed significant improvement in markers of vascular health (an increase in FMD and a decrease in both blood pressure and cIMT)[37]. In a 12-month prospective study involving nonpharmacological and pharmacological therapy in adolescents with primary hypertension, reductions in subclinical arterial injury (expressed as cIMT and carotid wall remodelling) and a decrease in waist circumference and inflammatory markers (namely high-sensitivity C-reactive protein levels) were significant predictors of improvement[38]. There is also evidence that EVA can be reversible among populations at higher risk, such as children with chronic kidney disease (CKD), when blood pressure and metabolic risk factors are well controlled[39].

Improved Risk Stratification and Individualised Goals for Blood Pressure Control

The blood pressure values defining hypertension must be seen as a threshold above which CVD risk increases dramatically, as it is well known that the association between blood pressure and cardiovascular risk develops as a continuum even within the range of values considered normal[40]. More importantly, recent evidence from clinical trials supports that higher-risk hypertensive adults or adults with certain comorbidities (established coronary heart disease, CKD and 10-year risk of atherosclerotic CVD ≥15%) benefit from attempting to achieve lower blood pressure targets (intensive treatment) than their hypertensive peers at lower cardiovascular risk strata (standard treatment). In brief, blood pressure targets may be tailored according to baseline CVD risk stratification[41]. In the same way as adults, children and adolescents with high blood pressure and CKD can also be treated to achieve lower blood pressure levels than their peers without CKD[42]. More recently, a post-hoc analysis of a randomised trial of intensive BP control versus standard BP control found a significant correlation between estimated PWV reduction and lower risk of all-cause mortality, both in intensive and standard treatment groups, with greater benefits found in the intensive treatment arm[43]. In the same analysis, outcome prediction based on estimated PWV was independent of Framingham Risk Score, which includes blood pressure; thus supporting vascular health evaluation as a useful tool to assess target organ damage and vascular dysfunction, beyond controlling blood pressure and other traditional risk factors[43]. Newer therapeutic approaches to hypertension include vascular health assessment to address the best time to initiate anti-hypertensive therapy, dosing, treatment targets, and follow-up.

Promoting Vascular Health as a Strategy to Improve Outcomes

Aiming to achieve ideal cardiovascular health should be based on both prevention and treatment. Lifestyle measures and pharmacological treatment of hypertension and other CVD risk factors represent the current approach of cardiovascular medicine to EVA. Lifestyle changes should include dietary interventions, together with physical activity, and avoidance of risk behaviours (such as smoking)[6,38]. Both cross-sectional and prospective observational studies suggest that individuals who usually engage in higher levels of physical activity have reduced arterial stiffness compared to those with a sedentary lifestyle. More specifically, aerobic exercise seems to be the modality associated with the greatest improvement in arterial stiffness, and the effect is further enhanced with higher aerobic exercise intensity and in participants with higher baseline arterial stiffness[44]. However, these findings may not be general for all risk groups. For instance, training exercise has not shown favourable effects in individuals with isolated systolic hypertension, probably due to the presence of irreversible arterial stiffening in this specific patient population. As a result, aerobic exercise seems to be an effective strategy in prevention rather than a treatment[45,46]. A systematic review of 38 studies evaluating the effects of dietary and nutrient interventions on arterial stiffness suggests that intake of omega-3, fish oils, soy isoflavones, and fermented

dairy products may be beneficial, while salt and caffeine intake may worsen arterial stiffness[47]. Combined lifestyle interventions involving aerobic exercise, the Dietary Approaches to Stop Hypertension (DASH) pattern and weight loss are likely to yield greater benefits in vascular health, despite being more challenging in terms of adherence[46]. Regarding pharmacological interventions, blood pressure control has the most evidential support. A meta-analysis that included 15 randomised, placebo-controlled trials reported a significant reduction in cfPWV among adult patients treated with anti-hypertensive drugs (angiotensin-converting enzyme inhibitors [ACEi], calcium channel blockers, diuretics and beta-blockers) and found ACEi to have the strongest effect[48]. It is noteworthy that the beneficial effect seems to mainly depend on the level of blood pressure control. Other therapeutic options include acetylsalicylic acid and anti-inflammatory drugs, although data on their potential to improve vascular health is less consistent across studies compared to the evidence that supports the use of anti-hypertensive drugs[11]. Studies in adults also support the use of statins to slow the progression of arterial stiffness[49,50]. In the paediatric population, there is also data suggesting the role of statins in reducing arterial stiffness and improving endothelial function, especially in high-risk subgroups, such as adolescents with dyslipidaemia[51] and children with type 1 diabetes[52]. Finally, three classes of antidiabetic drugs (GLP-1R agonists, SGLT-2 inhibitors, and metformin) seem to be able to improve arterial stiffness in adult patients with type 2 diabetes[53–55]. In summary, there is growing evidence that improving vascular health is feasible and may correlate with better clinical outcomes. Given the exceptionally low rate of major adverse cardiovascular events during childhood, the use of surrogate biomarkers predictive of future CVD may be acceptable as an alternative endpoint in clinical trials with paediatric subjects and may help clarify the role of these tools in guiding the treatment of children and adolescents.

CONCLUSION

Poor vascular health is an early sign of CVD in children and adolescents with high blood pressure and hypertension. It persists into adulthood and predicts worse cardiovascular outcomes, including mortality. As vascular phenotypes (EVA, HVA, and SUPERNOVA) improve traditional CVD risk stratification, implementing vascular health assessment in clinical practice may help further individualise cardiovascular medicine. Simplifying the methods used to study vascular health is crucial to help transfer this assessment from bench to bedside. A better understanding of the mechanisms underlying EVA may provide new targets for the treatment of hypertension, while the pathways underlying HVA and SUPERNOVA may reveal new strategies for protection against CVD. Increasing evidence supports the role of non-pharmacological and pharmacological strategies in slowing or even reversing vascular ageing. Finally, the concept of vascular age, as an aggregate measure of an individual's overall cardiovascular risk compared to peers of the same chronological age, may help clinicians communicate better with patients and their families, as it provides a more intuitive notion of CVD risk. Raising awareness about CVD risk is key to reducing its burden and helpful in younger and lower-risk populations.

Funding

Not applicable.

Acknowledgements

Not applicable.

Conflicts of interests

Nothing to disclose.

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