European Journal of Preventive Cardiology

ESC European Society of Cardiology

Invited editorial

European Journal of Preventive Cardiology
2018, Vol. 25(1) 100–102

DOI: 10.1177/2047487317743046
journals.sagepub.com/home/ejpc

SAGE

Arterial stiffness in childhood: A predictor for later cardiovascular disease?

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Arterial stiffness is known as an important surrogate marker of vascular damage and a strong predictor of cardiovascular disease (CVD).[1] Age-related degenerative changes in the intima of large elastic arteries contribute to the loss of arterial elastin and to increased arterial stiffness. Although arterial stiffness is strongly associated with ageing and is clinically shown mostly in older individuals, preclinical phases can occur in early childhood.[2]

Studies in children have shown a progressive increase in arterial stiffness by measuring the carotid intima-media thickness during childhood, indicating a structural alteration to the arterial wall starting already in early life.[2] Other studies investigating arterial stiffness used different non-invasive functional measurements of arterial stiffness, such as pulse wave velocity (PWV) or ambulatory arterial stiffness index. As arterial stiffness directly increases blood pressure, systolic blood pressure (SBP) has also been used as an indirect measure of arterial stiffness.[2]

Several factors and diseases have been shown to contribute to arterial stiffening in adults.[3] However, determinants of arterial stiffness at young age are not clear. Recently, height was identified as an important determinant of preschool arterial stiffness.[4] Moreover, CVD risk factors such as hypertension, obesity, diabetes and metabolic syndrome have been previously shown to contribute to arterial stiffening in young people.[5]

Previous studies showed a higher arterial stiffness in patients with congenital heart disease (CHD).[6] It has been hypothesized that patients with CHD have increased arterial stiffness already at an early age; and that this early vascular stiffening predisposes children to premature myocardial remodelling and cardiac damages later in life.[7] Recently, Muller and colleagues from the Technical University of Munich presented a study investigating the frequency of arterial stiffness in children with CHD.[8] They analysed central SBP as a measure of arterial stiffness in children aged 6–18 years with CHD ($n = 417$) and compared the results with an age- and gender-matched control group ($n = 1466$). This study revealed that children with CHD have significantly higher central SBP compared with the control group (102.1 ± 10.2 *vs.* 100.4 ± 8.6 mmHg, p-value < 0.001, respectively). The results also showed that among different subsets of children with CHD, central SBP was higher in subjects with left heart obstructions, transpositions of the great arteries after arterial switch, or with univentricular heart after total cavopulmonary connection, as compared with children in the control group. However, drawing firm conclusions from epidemiological studies assessing arterial stiffness in children with CHD is difficult, mainly due to the different methods applied. Some studies only assessed certain diagnostic subgroups, which makes comparison within various CHDs impossible. Using different devices and, more importantly, choosing between peripheral or central SBP may also result in different values and thereby different study results.[9]

The study performed by Muller and colleagues is a methodologically well-designed study and the contribution of this research study in childhood CVD preventive programme is timely. Control subjects were matched by age and gender, and the same methods were used to quantify arterial stiffness in children with and without CHD. This study used central SBP as a measure of arterial stiffness, which is considered a better predictor than peripheral SBP.[10] The Mobil-o-Graph device used in this study is a validated oscillometric measurement tool for non-invasive measurement of the central SBP, according to the British Hypertension Society and the European Society of Hypertension recommendations. Given that there is a strong positive association between hypertension and arterial stiffening, it seems logical to evaluate central SBP as a proxy of arterial stiffness in children. Nevertheless, it remains only a proxy and future studies

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should incorporate PWV, which is the gold standard way to non-invasively measure arterial stiffness according to the American Heart Association.

Several biases might have jeopardized the internal validity of this study. *Selection bias* is hard to rule out in epidemiological studies; in this study, children with CHD were recruited at their regular outpatient visit in Munich and asked to participate, and control subjects participated in a cohort of school children in the Munich area and were measured around the same time period; therefore, selection bias seems unlikely. However, as children with CHD were admitted from a tertiary centre where patients with greater severity are visited, the result of this study might not be easily generalizable to most children with CHD. Moreover, as children in the control group are assumed to not be familiar with medical devices and the hospital environment, the resulting tension may lead to higher blood pressure (BP) values at the time of measurements; consequently, the reported difference in central SBP between children with CHD and the control group might have been underestimated, thus resulting in misclassification bias. This study may also have been limited by indication bias; meaning that compared with the reference group children with CHD are more likely to develop hypertension. The correct BP measurement depends on the correct technique and the methods applied. As stated in this study, the central SBP value relied on a single pulse wave analysis, though obtaining a more accurate measurement requires a repeated measurement under controlled environmental conditions and by a trained professional. Additionally, this study was limited in assessing the potential effect modification of gender due to the small number of patients in each CHD subgroup; as the CVD risk profile in girls, such as body mass index and cholesterol level, is different, gender-stratified analysis might have given insight into potential different associations among girls and boys. Finally, confounding bias is one of the major concerns in epidemiological research. Although the analyses were adjusted for several confounding variables, the possibility remains that some unmeasured factors, for example, genetic variants, pubertal status, obesity, birth weight, diet or smoking, caused residual confounding. Specifically, this study lacks information on puberty hormones and on overweight, which are important factors in determining arterial stiffness.[11,12]

Implications and future studies

As CHD is associated with arterial stiffening already in childhood, the outlook for early CVD events is alarming among this population. Early detection of arterial dysfunction in children with CHD, but also in children in the general population, may provide a window for early treatment or lifestyle modifications to prevent CVD. We believe that it is time to move on to a more comprehensive evaluation and management of paediatric cardiometabolic risk factors, such as hypertension and obesity, to optimize prevention of later CVD.

Whether improvements in childhood arterial function are translated into long term clinical benefits and cardiovascular health particularly in high risk paediatric populations should be clarified. Through a longitudinal follow-up study, further work on the effect of cardiometabolic risk factors on improving early CVD taking potential confounders into consideration is warranted. Whether arterial stiffness is inherent and genetic factors are operative and whether arterial stiffness is caused by CHD are also pivotal research questions that should be answered. Moreover, future diagnostic research on the long-term consequences of interventions such as promoting a healthy lifestyle, pharmacological interventions, or surgery using ballooning or stent treatment in different subsets of children with CHD is of major interest.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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