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Review article

Methods to evaluate arterial structure and function in children – State-of-the art knowledge

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ABSTRACT

Background: With increasing rates of hypertension, obesity, and diabetes in the pediatric population, wide available, and reproducible methods are necessary to evaluate arterial structure and function in children and adolescents.
Methods: MEDLINE/Pubmed was searched for articles published in years 2012–2017 on methodology of, current knowledge on, and limitations of the most commonly used methods to evaluate central, proximal and coronary arteries, as well as endothelial function in pediatric patients.
Results: Among 1528 records screened (including 1475 records from years 2012 to 2017) 139 papers were found suitable for the review. Following methods were discussed in this review article: ultrasound measurements of the intima-media thickness, coronary calcium scoring using computed tomography, arterial stiffness measurements (pulse wave velocity and pulse wave analysis, carotid artery distensibility, pulse pressure, and ambulatory arterial stiffness index), ankle-brachial index, and methods to evaluate vascular endothelial function (flow-mediated vasodilation, peripheral arterial tonometry, Doppler laser flowmetry, and cellular and soluble markers of endothelial dysfunction).
Conclusions: Ultrasonographic measurement of carotid intima-media thickness and measurement of pulse wave velocity (by oscillometry or applanation tonometry) are highly reproducible methods applicable for both research and clinical practice with proved applicability for children aged ≥6 years or with height ≥120 cm. Evaluation of ambulatory arterial stiffness index by ambulatory blood pressure monitoring is another promising option in pediatric high-risk patients. Clearly, further studies are necessary to evaluate usefulness of these and other methods for the detection of subclinical arterial damage in children.

Contents

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1. Introduction

Cardiovascular causes are the most common cause of mortality among adults [1]. Adverse processes leading to arterial wall dysfunction begin already in early childhood. Intimal fatty infiltration was shown to be present in nearly all children by 3 years, and atherosclerotic plaques are detected in coronary artery walls already in adolescents [2]. At the same time, arterial elastic content decreases with age, with replacement of elastic fibers with criss-crossing collagen fibers, which changes elastic wall properties and leads to impaired peripheral perfusion [3].

Regardless of these natural age-related changes, some children are at risk of progression of blood vessel damage, and thus their cardiovascular risk is much increased compared to that in healthy peer. These mostly included children with homozygous familial hypercholesterolemia, congenital heart disease, after heart transplantation, with diabetes type 1 and 2, obesity, hypertension, metabolic syndrome, chronic kidney disease, post-neoplasm treatment survivors [4]. Because of great rarity of hard outcomes in children with concomitant increasing number of children with elevated cardiovascular risk there is clear need to evaluate surrogate, intermediate markers of cardiovascular damage in pediatric population. Stratification of cardiovascular risk in these patient groups requires use of validated, reproducible, and easily available methods to evaluate the condition of arterial vessels. In the recent years, the experience with the use of methods to evaluate arteries in children increased, some of these methods were introduced to routine clinical practice and their availability increased. Most importantly, reference values were established that allow interpretation of the results in the pediatric context.

In the European guidelines for the management of hypertension in the adults, measurements of pulse pressure, carotid intima-media thickness (cIMT), pulse wave velocity, and ankle-brachial index were recommended to evaluate subclinical arterial changes [5]. At present, there are no clear recommendations regarding the use of these methods in the pediatric population.

As number of different methods evaluating vascular health is constantly growing without clear recommendations regarding the use of these techniques in pediatric patients, there is a necessity to review current knowledge and experience on this topic. Thus, the aim of this review paper is to describe the methodology, limitations, and current pediatric experience in the most commonly used methods to evaluate central, proximal, and coronary arteries.

2. Material and methods

2.1. Literature search and data extraction

MEDLINE/Pubmed database (United States National Library of Medicine National Institutes of Health) was systematically searched up to February 2017 (last database search 14th February 2017) independently by both authors. A search was carried out with following PubMed MeSH terms in order to select the data existing in the literature: ((children[Title/Abstract] OR pediatric [Title/Abstract])) AND (intima-media[Title/Abstract] OR arterial structure[Title/Abstract] OR arterial function[Title/Abstract] OR arterial stiffness[Title/Abstract] OR endothelium[Title/Abstract]). The search was limited to studies published in last 5 years (2012–2017). A total of 1475 citations were found in MEDLINE/PubMed. The authors focused primarily on articles on reliable normative pediatric reference values, methodology, applicability in pediatric high-risk patients, and possible differences between adults and children. PRISMA flow chart (Fig. 1) shows process of inclusion of pediatric clinical trials into the final analysis [6]. As shown in Fig. 1, 1475 records from years 2012 to 2017 were screened. Both investigators independently screened all articles for those meeting the broad inclusion criteria. Both authors independently assessed the methodological quality of each selected article and applicability for this review. No attempt was made to mask the author's name or the journal's name. Any disagreement was resolved by consensus. 1018 records were excluded because they were written in other than English language, they contained data regarding diseases not relevant for this review, they were adult articles, review/systematic review/meta-analyses articles without new data, case reports/case series or because they were comments on other articles. Thus, 457 full-texts were assessed for eligilibilty. Among them 421 were also excluded because of not complete, out-of-date, or irrelevant for the review results or due to very small patient sample (<20 subjects). Therefore, 36 original pediatric papers from years 2012 to 2017 with available data remained. The authors evaluated also the possible presence of additional studies by means of a hand search of the bibliographies from the primary studies, review articles and key journals finding additional 53 older pediatric clinical studies relevant for the review. In addition to these 89 pediatric original papers both authors have added further 16 pediatric articles: 8 pediatric guideline/recommendation articles and 8 pediatric review papers. Due to fundamental significance 32 articles focusing on adult patients and 1 experimental (animal) paper were included into the final review. All adult articles were independently analyzed by both authors in terms of their applicability for this pediatric review.

3. Review

3.1. Arterial structure

3.1.1. Carotid intima-media thickness

Measurement of cIMT is an established marker of structural changes in large arteries [7]. An increase in cIMT is believed to reflect early arterial changes that ultimately result in formation of an atherosclerotic plaque.

The recommendations for ***measurement of cIMT*** in pediatric patients were published by American Heart Association (AHA) [8], and by Association for European Paediatric Cardiology (AEPC) [9]. The measurement is performed in the supine position with head usually tilted contralaterally at 45°, using a high-frequency linear ultrasound probe (7–12 MHz) with a "footprint" of 3–4 cm [8,9]. The long axis of the artery should be as parallel to the probe surface as possible. The measured cIMT depends on the acquisition angle. Thus, some authors advocate the use of a special device to evaluate the angle between the probe and the long axis of the body. The measurement is usually performed within the distal wall of the common carotid artery, most commonly 10 mm below the carotid bulb, although it is also possible to measure the internal carotid artery within its proximal 10 mm or the bulb itself. Two-