Variation of the brachial artery diameter in obese children: present and future

Variação do diâmetro da artéria braquial em crianças obesas: presente e futuro

Variación del diámetro de la arteria braquial en niños obesos: presente y futuro

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ABSTRACT

Objective: Literature review on the use of the variation measure of the brachial artery diameter by high-resolution ultrasound (flow-mediated dilation) as a predictor of cardiovascular disease risk in children and adolescents.

Data source: Survey of studies indexed in Medline/Pubmed, which were published between 2002 and 2011 using the following keywords in various combinations:"endothelium," "child", "ultrasonography" and "obesity", as well as classic texts on the subject. We found 54 publications and 32 were included in this review.

Synthesis of data: The study of endothelial dysfunction has been used as a predictor of risk for cardiovascular diseases such as atherosclerosis and coronary heart disease, since endothelial injury is an important event in the physiopathology of these diseases.

Conclusions: The flow-mediated dilation of the brachial artery seems to be important as a diagnostic and prognostic tool to assess endothelial function in children and adolescents who are overweight, because it is a noninvasive method with good profile regarding cost, safety, and benefits.

Key-words: endothelium; child; ultrasonography; obesity.

RESUMO

Objetivo: Revisão da literatura acerca do uso da medida da variação do diâmetro da artéria braquial por ultrassonografia de alta resolução (dilatação mediada por fluxo) como preditor de risco para doença cardiovascular em crianças e adolescentes obesos.

Fontes de dados: Levantamento de publicações indexadas no Medline/PubMed de trabalhos publicados entre 2002 e 2011, rastreadas com a combinação dos descritores: "*endothelium*", "*child*", "*ultrasonography*" e "*obesity*", além de estudos e textos clássicos sobre o tema. Foram encontradas 54 publicações e 32 delas foram incluídas na presente revisão do tema.

Síntese dos dados: O estudo da disfunção endotelial tem sido empregado como preditor de risco para doenças cardiovasculares, tais como aterosclerose e doença cardíaca coronariana, visto que a lesão endotelial é um importante evento na fisiopatologia de tais doenças.

Conclusões: A dilatação mediada por fluxo da artéria braquial mostra-se importante como ferramenta diagnóstica e prognóstica na avaliação da função endotelial de crianças e adolescentes com excesso de peso por ser um método não invasivo, com boa aplicabilidade quanto ao custo, à inocuidade e ao benefício.

Palavras-chave: endotélio; criança; ultrassonografia; obesidade.

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RESUMEN

Objetivo: Revisión de la literatura sobre el uso de la medida de la variación del diámetro de la arteria braquial, por ultrasonografía de alta resolución (dilatación mediada por flujo), como predictor de riesgo para enfermedad cardiovascular en niños y adolescentes obesos.

Fuentes de datos: Inventario de publicaciones indizadas en Medline/Pubmed de trabajos publicados entre 2002 y 2011, buscadas mediante la combinación de los descriptores: «*endothelium*», «*child*», «*ultrasonography*» y «*obesity*», además de estudios y textos clásicos sobre el tema. Se encontraron 54 publicaciones y 32 de ésas fueron incluidas en la presente revisión del tema.

Síntesis de los datos: El estudio de la disfunción endotelial viene siendo empleado como predictor de riesgo para enfermedades cardiovasculares, tales como aterosclerosis y enfermedad cardíaca coronariana, puesto que la lesión endotelial es un importante evento en la fisiopatología de tales enfermedades.

Conclusiones: La dilatación de la arteria braquial mediada por flujo se muestra importante como herramienta diagnóstica y pronóstica en la evaluación de la función endotelial de niños y adolescentes con exceso de peso, por ser un método no invasivo, con buena aplicabilidad respecto al costo, a la inclusión y al beneficio.

Palabras clave: endotelio; niño; ultrasonografía; obesidad.

Introduction

It is known that excess weight is currently the sixth most important risk factor for development of diseases[1]. The complex pathological process underlying obesity reflects environmental and genetic interactions[1,2]. Environmental factors that can contribute to reducing the impact of excess weight on children and adolescents include sociodemographic variables and lifestyle factors that are potentially modifiable through healthy nutrition and engaging in physical activity[2,3].

The obesity epidemic has been growing since 1980, in both developed and developing countries, but it was only in 1997 the World Health Organization (WHO) classified it as an important public health problem that should be monitored from childhood[4,5]. Overweight children exhibit risk factors for cardiovascular diseases (CVD) such as hypertension, dyslipidemia, glucose intolerance and vascular disorders. Excessive weight in childhood can increase the likelihood of developing coronary disease in adulthood as a result of the early effects of these risk factors[6]. Damaged endothelium plays and important role in the development of several CVDs[7], such as atherosclerosis and coronary disease[7,8], and is used as a predictor of the risk of these events[9,10].

The endothelium performs its function through the action of a variety of different molecules in response to a range of physical and chemical stimuli, including hypoxia, acetylcholine, bradykinin, serotonin and increased blood flow. Production and release of nitric oxide (NO) by endothelial cells have been identified as the principal vasodilation mediating mechanisms and this has been demonstrated in both *in vitro* and *in vivo* experiments[11,12]. This means that poor regulation of NO production and release is one of the principal factors in endothelial dysfunction. It is believed that endothelial dysfunction may be involved in the pathophysiology of CVD and metabolic diseases in children[13-15] and adolescents[16-18] with severe obesity.

Several methods have been tested for analyzing endothelial function, one of which, high resolution ultrasound measurement of variation in brachial artery diameter (flow-mediated dilation – FMD), is a noninvasive method that has been widely used in research and correlated with clinical practice for the last two decades[19]. The importance of studying intermediate markers for analysis of endothelial function, particularly in high risk groups, means that research into noninvasive ultrasound techniques such as brachial artery FMD has become a focus of efforts to correlate vascular function with CVD and increased morbidity and mortality in affected populations.

The objective of this study was to conduct an up to date bibliographic review of the application of FMD for assessment of obese children, with emphasis on the technique's importance in nutrology and pediatric practice. This article is based on the results of a literature search conducted on Medline/Pubmed for studies published from 2002 to 2011, using the keywords "obesity and ultrasonography and child and endothelium" in addition to classic studies and texts that address the subject. Fifty-four articles were identified, of which 32 were chosen that fitted the study objectives.

Study of endothelial function

Atherosclerosis is a systemic arterial disease in which damaged endothelium promotes the entry of circulatory inflammatory cells, initiating a process of localized fibrosis and lipid

deposition[20]. This is a diffuse process of the artery walls and its natural history of development includes an asymptomatic stage that can have onset in childhood or adulthood and can lead to luminal stenosis or sudden occlusion of an artery by unstable lesions, causing clinical events[21].

Endothelial dysfunction is the primary event in development of atherosclerosis and can be detected long before the appearance of structural atherosclerotic disease[19,21,22]. The endothelium used to be recognized only as a physical barrier, part of the artery wall, but it is now known that it has countless autocrine, paracrine and endocrine properties and, since it takes part in vascular homeostasis, influences vascular tonus, cell growth, fibrinolysis, thrombolysis and inflammatory and immune responses[23,24].

Under physiological conditions, the endothelium acts as a potent vasodilator and leukocyte adhesion inhibitor and is active in smooth muscle cell growth and platelet aggregation. Many different biologically active molecules take part in these physiological mechanisms, such as NO produced by enzymes known as nitric oxide synthases, activated by increased blood flow (shear stress), hypoxia, acetylcholine and bradykinin[23,25].

Cardiovascular risk factors like atherosclerosis, arterial hypertension, diabetes mellitus and smoking appear to be linked to a loss of endothelial functional integrity[19,26]. Endothelial dysfunction is manifest in reduced NO production and can be exacerbated by constrictive factors, such as endothelin. There is therefore an increase in vasoconstriction responses, in vascular smooth muscle cell proliferation and migration and in expression of adhesion molecules and platelets[27]. Dysregulation of NO production and release is the primary factor in endothelial dysfunction. It is believed that endothelial dysfunction may be involved in the pathophysiology of vascular and metabolic diseases in hypertension and metabolism-related disorders and obesity[5,13,17,28], including in obese children[13-15] and adolescents[16-18].

Countless methods for assessing endothelial function have been investigated, both invasive, such as angiography, intravascular ultrasonography and intra-arterial infusion of selective endothelial agonists, and noninvasive, such as measuring variation in brachial artery diameter (FMD) and plethysmography. From a practical point of view, noninvasive techniques are of greater interest because they are less expensive, harmless and offer potential benefits. Foremost among the noninvasive methods is measurement of brachial artery FMD using high-frequency echography, which was described in 1989 by Anderson and Merck and has been used in research applications since 1992[19].

Childhood Obesity and Cardiovascular Risk

Over the last few decades, childhood obesity has come to be considered a public health problem in both developed countries and those in development. The consequences are similar to those observed in adults, including hypertension, dyslipidemia, chronic inflammation, hyperinsulinemia and endothelial dysfunction. Among adolescents and young adults who had died of traumatic causes, risk factors for CVD were identified and correlated with asymptomatic atherosclerotic disease, and it was found that lesions were more advanced in obese individuals[29].

The anthropometric-nutritional profile of the Brazilian population has changed over the last thirty years, with increasing overweight and obesity, which is a phenomenon known as epidemiological transition[4]. Nutritional behavior during childhood has a direct influence on dietary habits in adulthood and, as a result, obese children are more likely to become obese adults[30]. It is known that children and adolescents with excess weight are at increased risk of adverse health events over both the short term and long term. These include increased risk of early development of CVD and the metabolic abnormalities associated with them, such as arterial hypertension, hypercholesterolemia, hypertriglyceridemia, insulin resistance syndrome and vascular disorders, such as increased carotid thickness[5-6,14,30,31]. All of these factors increase the cost of healthcare to society[31].

It has been suggested that prenatal exposure or exposure in early life confers an increased risk of excess weight in later phases of life. In this context, excess weight, and particularly abdominal fat, is a recognized risk factor for CVD, adult onset diabetes mellitus, cerebral vascular accidents and death[32].

As nutritional transition progresses, obesity affects people at ever younger ages and its effects appear ever earlier. This being so, it is important that high-risk populations be monitored, preferably using noninvasive methods, so that preventative measures and public health policies can be implemented as early as possible.

Technical Aspects of Flow-mediated Dilation

The technique was first described by Anderson and Merck (1989) and has been used in clinical research since 1992[19]. It has since been widely adopted for assessment of endothelial function[21,26,33-35]. As a result, it became necessary to standardize the technique to provide uniform results that would allow comparison of the results found at different research centers[34].

Vascular reactivity means that countless factors affect FMD, including ambient temperature, foods, drugs, the menstrual cycle, sympathetic stimuli and physical and emotional stress, among others. All of these factors must be controlled for before the test is run, and it should be performed between seven and nine o'clock in the morning[34-35].

To correctly execute the technique, the operator must be trained in two-dimensional and Doppler ultrasound and must be equipped with a high-resolution ultrasound machine coupled to an electrocardiogram (ECG). There is a steep learning curve to surmount and observers should conduct at least 100 procedures under supervision[34]. This degree of rigor is necessary because the low magnitude of the variation in brachial artery diameter before and after compression of the forearm means that intraobserver and interobserver reproducibility is experience-dependent and easily compromised[33].

In 2005, Bots *et al* conducted a meta-analysis of publications on FMD from 1991 to 2002, covering 219 studies and 16,680 subjects, assessing details such as type of equipment, location of compression and point of brachial artery measurement, duration of occlusion, post-occlusion measurement time and pressure exerted during compression with the sphygmomanometer. They observed a great deal of variation between studies in terms of FMD results (ranging from -1.9 to 19.2%), resulting from the different techniques employed and highly differentiated study samples[36].

The measurement location (upper arm or forearm) did nor significantly affect FMD measurements taken with different techniques[36]. The majority of the current studies preferred to measure the brachial artery longitudinally, from the anterior, above the antecubital fossa[37-42]. Occlusion times of approximately 5 minutes provoked significant variation in vascular diameter[36]. The post-occlusion measurement time that provoked the most significant increase in artery diameter was 60 seconds, which was the interval chosen in the majority of studies[42]. A high-resolution linear transducer is used to view the brachial artery longitudinally and measurements are taken before and after compressive stimulus, as shown in Figure 1.

Brachial Artery Flow-Mediated Dilation, Children and Obesity

While the clinical complications of atherosclerosis do not emerge until adulthood, or even old age, atherosclerotic disease is a lifelong process that has its roots in childhood. Improvements in noninvasive imaging methods, in particular ultrasonography, have made it possible to assess the endothelial health of asymptomatic children, with or without cardiovascular risk factors[43].

Abnormal arterial compliance can suggest subclinical atherosclerosis since it indicates the presence of arterial rigidity and calcification, compromised endothelial function and increased carotid intima-media thickness. In children and adolescents, arterial compliance has been investigated using noninvasive methods and its link with the risk of

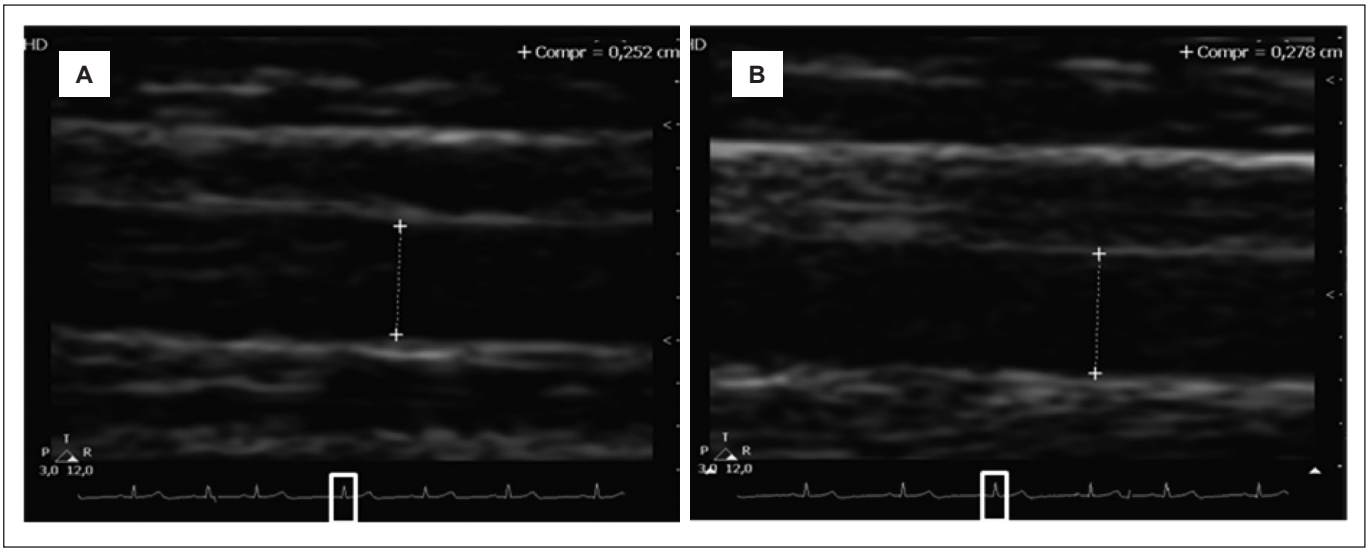

Figure 1 - High resolution linear ultrasound measurement of brachial artery diameter before stimulus (A) and 60 seconds after 5 minutes with forearm compressed (B). Observe the measurement coinciding with the electrocardiogram QRS complex. Flow-mediated dilation (%) = diameter A – diameter B / diameter A x 100

developing CVD has been explored. Invasive techniques, such as coronary angiography, used to diagnose diagnosis coronary artery stenosis, cannot assess arterial functional reactivity[44-45].

Countless methods have been tested for assessing endothelial function in the pediatric population with a view to defining prognosis and cardiovascular risk, but FMD and studies of the carotid intima-media thickness are the most widely used. Scientific publications have demonstrated correlations between pediatric diseases and abnormalities of endothelial function detected by FMD[5,43,46-48].

Woo *et al* studied 82 obese children aged between nine and 12 to assess the degree of reversibility of early arterial damage. The children were randomly assigned either to an intervention entirely based on diet or to one with a dietary component plus a structured program of physical exercises lasting initially for six weeks and then for one year, with the objective of defining potentially effective strategies that could improve obesity linked with vascular disorders. They assessed endothelial function using FMD and carotid artery intima-media thickness and analyzed a range of anthropometric parameters and laboratory results. They concluded that obesity linked with vascular dysfunction in healthy children was partially reversible with the dietary intervention alone or with the dietary intervention and physical training for six weeks and that the diet and physical exercise together for one year led to sustained improvement[48].

Childhood obesity appears to contribute to development and progression of premature atherosclerosis, particularly when combined with hypertension and dyslipidemia. Zhu *et al*[5], demonstrated this in a study with obese and non-obese school-aged children, assessing carotid artery intima-media thickness, FMD and biochemical markers of dyslipidemia. They found that carotid thickness was significantly greater (0.62 *vs.* 0.46 mm, $p<0.001$) and FMD was reduced (10.9 *vs.* 18.8%) in the obese group, revealing the correlation with endothelial dysfunction[5].

Several situations in pediatric practice have a correlation with reduced brachial artery FMD, including kidney diseases, childhood cardiac surgery, Kawasaki disease, dyslipidemia and homocystinuria[47]. Flow-mediated dilation results of less than 10 to 12% are linked with compromised endothelial function in pediatric groups[5].

Adolescents with a family history of CVD and familial hypercholesterolemia have lower FMD than healthy populations[49]. A negative correlation has been shown between FMD and low density lipoprotein (LDL) levels[50]. Reduced FMD has also been observed in prepubescent children with high blood pressure and in obese children with insulin resistance[51]. Obese children who are asymptomatic from a cardiovascular point of view, but have high body mass index (BMI), and abnormal glycemia, cholesterol and insulin levels have lower FMD than healthy children[52]. On the other hand, lifestyle changes, such as routine physical exercise and diet, are correlated with increases in FMD in both healthy and overweight children and adolescents[53]. Table 1 lists the principal indications for investigating endothelial function using brachial artery FMD in school-aged children.

Table 1 - Pediatric indications for investigating endothelial function by flow-mediated dilation of the brachial artery

	Indications
1.	Dyslipidemia
2.	Familial hypercholesterolemia
3.	Diabetes mellitus
4.	Obesity
5.	Chronic kidney diseases
6.	Homocystinuria
7.	Kawasaki disease
8.	Pediatric cardiac surgery

Early identification of the cardiovascular risk factors associated with excess weight in children and adolescents is important for development of educational interventions and prevention programs designed to target these factors, in order to reduce excess weight among children and improve the health and quality of life of the population.

Final comments

Brachial artery FMD is an important tool when investigating endothelial function in people with cardiovascular risk factors, since researchers and clinicians need an intermediate marker to enable them to intervene in the natural history of CVDs, in order to reduce morbidity and mortality among children, adolescents and adults. There are certain technical limitations to the method, since it requires a high-resolution ultrasound machine coupled to an ECG, mechanical apparatus and a properly trained operator, but it can prove an essential instrument for providing the clinical evidence to support intervention in a patient's lifestyle and health promotion.

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