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Feasibility of very-high resolution ultrasound to assess elastic and muscular arterial wall morphology in adolescents attending an outpatient clinic for obesity and lipid abnormalities

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ABSTRACT

Objective: Atherosclerosis begins during early life and is accelerated in individuals with cardiovascular risk factors. We hypothesized that very-high resolution ultrasound (VHRU, 25–55 MHz) could feasibly detect early arterial changes in adolescents with risk factors.
Methods: We prospectively imaged the carotid, brachial and radial arterial morphology (far wall intima–media thickness, IMT; adventitia thickness, AT) by VHRU in 58 youths (age 14 ± 2 years) attending a Pediatric Preventive Cardiology Clinic for assessment and management of cardiovascular risk factors and compared the findings to those from an age-matched group of 67 controls.
Results: Brachial and radial imaging was successful for all subjects. The carotid far wall could not be imaged in 7% of the patients due to limitations in penetration. VHRU image quality was related to body size and imaging depth. Imaging and analysis time were 12 ± 3 and 18 ± 3 min, respectively. Carotid IMT was increased in patients (0.42 ± 0.05 vs. 0.40 ± 0.06 mm, $p = 0.05$). No differences were found in brachial or radial IMT or AT vs. controls. Age, male gender, body mass index, systolic blood pressure (BP), but not lipid levels, were associated with arterial IMT in regression analyses.
Conclusion: VHRU is feasible in imaging carotid and peripheral muscular artery IMT in adolescents. The arterial IMT is associated with age, gender, adiposity and systolic BP, but not lipid levels, in this adolescent population. Further studies including patients with manifest clinical atherosclerosis are needed to assess if VHRU has applications in atherosclerosis research.
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1. Introduction

The noninvasive assessment of intima–media thickness (IMT) of the carotid artery has become a surrogate marker of subclinical atherosclerosis in the adolescent pediatric population [1] and increased carotid IMT has been reported in clinical pediatric populations with familial hypercholesterolemia [2–5], type 1 diabetes [6], obesity with and without type 2 diabetes [7], hypertension [8], coarctation of the aorta [9], and chronic renal disease [10].

Conventional high-resolution vascular ultrasound by B-mode imaging (<15 MHz) is currently used to image the carotid arterial IMT in older children. The assessment of the peripheral vasculature and more detailed imaging of the different arterial wall layers are, however, precluded due to limitations in axial resolution. We have recently validated a noninvasive very-high resolution ultrasound (VHRU) method to assess the combined IMT, adventitia thickness (AT) and total wall thickness (intima–media–adventitia thickness, IMAT) of muscular arteries and IMT of elastic arteries using 25–55 MHz transducers [11]. VHRU allows studying the morphology of these arteries in almost microscopic detail and could potentially provide insights into the subclinical atherosclerotic process in an adolescent population with cardiovascular risk factors.

The basic physical dependence between axial spatial resolution, penetration and ultrasound frequency (i.e. pulse length), are well known. As a consequence, an increase in the imaging depth related to body size or overlying fat are commonly associated with limitations in ultrasound penetration. VHRU has limited penetrance and, therefore, allows noninvasive transcutaneous imaging of superficial structures only. Consequently, the highest ultrasound

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frequencies (and best axial spatial resolution) are only applicable for the most superficial peripheral arteries of the limbs [11]. There are, however, currently no studies on the feasibility of VHRU in terms of body size, frequencies applied, time of image acquisition or image analysis, and image quality in the clinical setting in a pediatric population. The main objective of this study was then to study the feasibility of VHRU and the secondary objective to further assess differences in arterial layer thickness in the carotid, brachial and radial arteries and their relation to family history, clinical status and blood pressure (BP) in an outpatient setting of adolescents referred to a Pediatric Preventive Cardiology Clinic for assessment and management of cardiovascular risk factors, primarily lipid abnormalities and/or obesity.

2. Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Research Ethics Board. The use of VHRU in human subjects was in addition approved by Health Canada. Study participation required written informed consent by all participants. No adverse effects of VHRU were observed.

2.1. Study design and populations

This is a prospective cross-sectional study. Fifty-eight adolescents (age 10–17 years) referred to a Pediatric Preventive Cardiology Clinic at the Hospital for Sick Children, Toronto, between July 2009 and April 2010 for assessment and management of cardiovascular risk factors, primarily lipid abnormalities and/or obesity, were recruited. An age-matched control group of 67 adolescents were recruited from nearby schools and among patients referred to the hospital for the assessment of an innocent murmur. None of the controls reported use of any medications or medical problems. A first generation family history of significant systemic hypertension, lipid disorder, diabetes, or smoking was assessed by interview. Patient information was abstracted from the hospital charts. Hypercholesterolemia was defined as total fasting plasma cholesterol more than 6.7 mmol/L and/or LDL-cholesterol more than 4.0 mmol/L. None of the clinic patients presented with tendon xanthomata. Genetic testing for familial hypercholesterolemia was not applied in the clinical setting and, therefore, possible familial hypercholesterolemia was defined according to the Simon Broome register group criteria [12].

All measurements were obtained on non-sedated healthy controls and patients at rest and in the supine position in the echo laboratory at the Hospital for Sick Children. Systolic and diastolic BP recordings were obtained from the right arm with appropriate sized cuffs following at least 30 min of rest using an oscillometric device (Dinamap, Criticon, Inc.). Three recordings were obtained and the mean of the lowest two were used in the analyses [13,14]. Height was measured with a stadiometer to the nearest 0.1 cm and weight with an electronic balance to the nearest 0.1 kg. The clinical characteristics of the patients and controls are shown in Table 1.

2.2. Vascular imaging

Ultrasound recordings from bilateral common carotid, brachial and radial arteries were obtained using the Vevo 770 ultrasound system (Visualsonics, Toronto, Canada) with mechanical 25 MHz (RMV710B), 35 MHz (RMV712), and 55 MHz (RMV708) linear transducers and stored for off-line analysis. Care was taken not to compress the vessels during image acquisition.

Bilateral common carotid arteries were studied 1 cm proximal to the carotid bulb, the brachial arteries 2 cm proximal to the cubital skin fold, and the radial arteries 1–2 cm proximal to the skin fold that separates the palma manus from the anterior antebrachial region. Measurements were made off-line on high-quality vascular images showing a good distinction between structural interfaces. End-diastolic and peak-systolic (carotid only) lumen dimensions were obtained with reference to the simultaneously recorded electrocardiogram. The combined IMT and IMAT were measured from the far wall with the leading edge technique during end-diastole as previously described [11] (Fig. 1). AT was calculated as the difference between IMT and IMAT for the radial and brachial arteries. The mean of three measurements was used in the analyses. The single observer (TS) was blinded to the study group and the clinical characteristics of the subjects. The accuracy and precision of the method have recently been reported [11]. The intra-, interobserver, and test-retest coefficients of variation for IMT were 7–9%, 9–19%, and 11–16% with 25–55 MHz, respectively. The intra, interobserver, and test–retest coefficients of variation for IMAT were 5–8%, 8–11%, and 14–15% with 25–55 MHz, respectively. The intra-, interobserver, and test–retest coefficients of variation for the calculated AT were 15–20%, 20–36%, and 24–35% with 25–55 MHz, respectively.

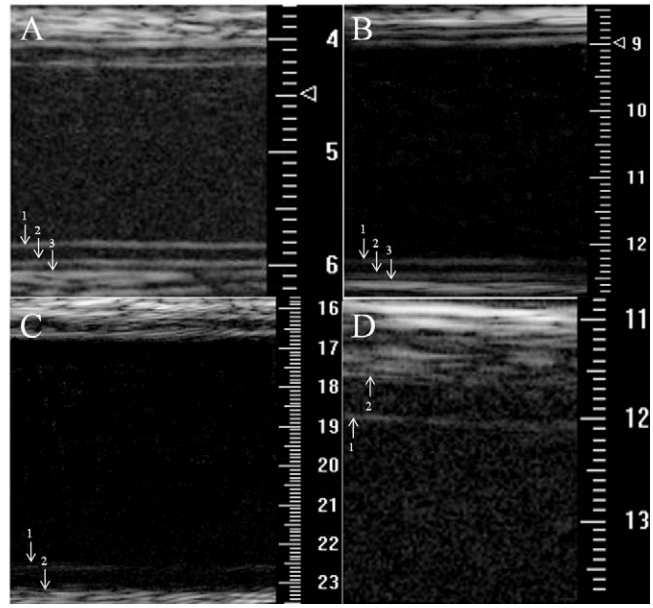

Fig. 1. Transcutaneous VHRU of the radial artery (A, 55 MHz), brachial artery (B, 35 MHz), common carotid artery (C, 25 MHz), and common carotid artery near wall (D, 35 MHz) in a 15-year-old obese male (BMI 30.4 kg/m^2, BMI z-score 2.03, RR 136/71 mmHg, normal plasma lipid levels). The scale is in millimeters. The radial and the brachial arteries display the triple line pattern and the carotid artery the double line pattern. The arrows mark the leading edge (or trailing edge for D) used in the measurement of arterial wall IMT and IMAT. [1] Internal elastic lamina, [2] External elastic lamina, [3] External vessel wall border.

The transducer frequency applied (55, 35 or 25 MHz) was recorded for each vessel imaged. The highest frequency transducer able to image the vessel far wall was applied. If the far wall was not observed in the image due to limited ultrasound penetration, the transducer was stepwise changed to a lower frequency transducer. If the far wall of the vessel was not observed with the lowest frequency transducer (25 MHz), then the near wall was surveyed. The depth from the skin to the leading edge of the lumen vessel interface of the far wall (or the trailing edge of the near wall) was measured to the closest tenth of a millimeter. Image quality was subjectively assessed in all images by a single investigator (TS) blinded to the clinical characteristics and graded as follows: 0, inadequate imaging including complete absence of vessel of interest due to limitations in penetration; 1, poor imaging including poor distinction between the layers of the far wall or near wall imaging only; 2, fair imaging including sufficient

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