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Non-Invasive Vascular Elastography as a One-Step Imaging Technique to Evaluate Early Vascular Changes in Children Compared to B-Mode-Based Intima-Media Thickness Technique : A Validation Study Using Inter- and Intra-Rater Reliability

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Abstract

Background: Childhood obesity is linked to higher adult mortality and morbidity from atherosclerosis. It is primordial to detect at-risk children earlier-on to prevent disease progression. Carotid intima-media thickness (IMT) is a subclinical radiological marker for early atherosclerosis. B-mode ultrasound is a known technique to assess IMT, but no gold standard technique exists in children. Non-invasive vascular elastography (NIVE) using speckle statistics is an innovative alternative to evaluate IMT and adds by providing translation, strain and shear strain measurements. Validation studies for both techniques lack in children. **Purpose:** Validate the reproducibility of the 2 techniques in Canadian children. **Methods:** We conducted a prospective study where anthropometry, blood pressure, IMT and elastography were measured. Six operators obtained 2 measurements for both carotid arteries using both techniques, for a total of 720 measurements. Inter- and intra-class correlation coefficients (ICC) were calculated for each measurement technique and elastography parameters. **Results:** 30 participants (13.0 ± 1.26 years, 17 girls) were recruited. Twelve were overweight. No significant difference was found in mean IMT between weight groups for either technique (P = .15 and P = .60). We found excellent inter- (ICC = .98 [95% Confidence Interval (CI): .97; .99]) and intra- (ICC = .90-.93) operator reliability for the B-mode technique, and good inter (ICC = .70 [95% CI: .47; .85]) and intra- (ICC = .71-.91) operator reliability for the NIVE-based technique. Poor reliability was found between techniques (ICC = .30 [95% CI: −.31; .65). For elastography parameters, translation was the most reliable (ICC = .94-.95). **Conclusion:** IMT measurement is reproducible in children but not between techniques. NIVE gives the advantage of evaluating elastography.

Résumé

Contexte : L'obésité durant l'enfance est associée à une plus grande morbidité et mortalité due à l'athérosclérose à l'age l'adulte. Il est primordial de détecter plus précocement les enfants à risque pour éviter la progression de la maladie. L'épaisseur intima-média (EIM) de l'artère carotide est un marqueur radiologique précoce d'athérosclérose. L'échographie mode B est une technique connue pour l'évaluation de l'EIM, mais il n'existe pas de technique de référence validée chez les enfants.

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L'élastographie vasculaire non invasive (NIVE) utilisant des statistiques de texture ultrasonore "speckle" est un moyen de substitution innovant pour l'évaluation de l'EIM en fournissant des mesures de translation, déformation et déformation de cisaillement. Il manque d'études de validation pour les deux techniques chez les enfants. **Objectif :** Valider la reproductibilité des deux techniques chez les enfants canadiens. **Méthodes :** Nous avons mené une étude prospective dans laquelle nous avons mesuré des données anthropométriques, de pression artérielle, d'EIM et d'élastographie. Six opérateurs ont obtenu deux mesures pour les deux artères carotides en utilisant les deux techniques; pour un total de 720 mesures. Les coefficients de corrélation inter et intraclasse (ICC) ont été calculés pour chaque technique de mesure et paramètres d'élastographie. **Résultats :** 30 participants (13,0 ± 1,26 ans, 17 filles) ont été recrutés. Douze participants étaient en surcharge pondérale. Aucune différence significative n'a été trouvée dans l'EIM moyenne entre les sous-groupes de poids pour chacune des techniques ($P = 0,15$ et $P = 0,60$). Nous avons trouvé une excellente fiabilité interopérateurs (ICC = 0,98 [intervalle de confiance [IC] à 95 % : 0,97; 0,99]) et intraopérateur (ICC = 0,90 à 0,93) pour la technique en mode B et une bonne fiabilité interopérateurs (ICC = 0,70 [IC à 95 % : 0,47 à 0,85]) et intraopérateur (ICC = 0,71 à 0,91) pour la technique basée sur NIVE. Une faible fiabilité a été trouvée entre les techniques (ICC = 0,30 ; IC à 95 % : −0,31 ; 0,65). Dans les paramètres d'élastographie, la translation a été la plus fiable (ICC = 0,94 à 0,95). **Conclusion :** La mesure de l'EIM est reproductible chez les enfants, mais pas entre les techniques. La technique NIVE offre l'avantage d'évaluer l'élastographie.

Keywords
pediatric, atherosclerosis, intima-media thickness, screening, elastography, cardiovascular

Introduction

Atherosclerosis begins in childhood with subtle vascular changes.[1] Obesity is linked to high mortality and morbidity.[2,3] Although the cardiometabolic sequelae of atherosclerosis from obesity do not appear until adulthood, at risk obese children tend to remain obese into adulthood.[4] The measurement of the intima-media thickness (IMT) of the common carotid artery has been useful for cardiovascular risk assessment in adults.[4] IMT is the thickness of the vascular wall measured from the lumen-intima interface to the media-adventitia interface.[5] Increased IMT is associated with many cardiovascular disease risk factors and represents a radiological marker for atherosclerosis.[6] Obese children have higher IMT values than healthy children, as well as adverse cardiovascular risk profiles.[6-9] Moreover, the ratio IMT/carotid-diameter considers body habitus in the evaluation of at-risk children.[10] In adults, this ratio represents vessel-remodelling secondary to intima-media thickening. The increase in diameter compensates for the shear stress of the blood flow against the weaker arterial wall due to atherosclerotic plaque.[10] Despite increased IMT, the ratio IMT/diameter is lower in obese participants compared to normal weight.[10]

A systematic review found a linear relationship between adiposity and IMT, meaning that time spent overweight is an important factor to consider when assessing cardiovascular risk.[8] Different measurement techniques exist in the literature, including manual, semi-automated and automated techniques, B-mode-based and radiofrequency-based approaches, but none are validated in children.[9] There is therefore possible heterogeneity in IMT values due to technique. Non-invasive vascular elastography (NIVE) is a new one-step exam evaluating IMT and vascular wall biomechanics for the diagnosis of early atherosclerosis in obese children and adults.[11,12]

Unlike adults, literature lacks normative tables in children, and techniques are not reliable.[6,13,14] Very few studies investigated inter- and intra-operator variability for IMT in children. NIVE technology detects IMT and mechanical vascular changes by measuring the cumulated axial strain (CAS), cumulated axial translation (CAT), cumulated lateral translation (CLT) and cumulated axial shear strain magnitude (C|ShS|) from a radiofrequency-based video.[15] The strains and translations are caused by the cardiac pulsation. Obese children tend to have significantly stiffer arteries.[16-19] Therefore, CAS, CLT, CAT and C|ShS| are altered in obese children with early atherosclerosis.[11,15] No reproducibility studies have been done for vascular elastography parameters, including NIVE in children.

We hypothesize that the techniques are not reliable beween each other but are reproducible between operators. The main objective of this study is to compare the reliability and reproducibility of B-mode-based IMT with NIVE-based IMT in healthy children. A secondary objective is to assess the reliability of NIVE parameters CAS, CLT, CAT and C|ShS| in the same population.

Methods

Study Design and Participants

A prospective study was conducted between October 2020 and June 2021 after IRB approval. Thirty children aged from 11.0 to 14.9 years old were recruited. Guidelines for reporting reliability and agreement studies (GRRAS) were followed.[20] To detect a difference of .1 mm between techniques with a power of 90% and an intra-class correlation coefficient (ICC) > .6 (.4 and .5 being the null hypothesis, due to random correlation), the required sample size was 30. Inclusion criterion was children of any weight. Exclusion criteria were cardiovascular disease, diabetes, congenital anaemia, systemic disease, acute abdominal condition, acute viral infection or post-transplant. Participants were recruited from the Radiology Department of the Sainte-Justine Children's Hospital (CHUSJ). Written informed consent and assent were obtained from every child and their parents or legal tutor. Anthropometric and blood pressure measurements were acquired. Body mass index (BMI) was calculated using the formula: weight (in kg) divided by height (in meters, then squared), and was calculated according to U.S Centers for Disease Control and Prevention Growth Charts. Waist and calf circumference, tricipital, subscapular and supra-iliac skinfolds were measured. Blood pressure was measured after a 5-minute rest in sitting position, on each arm once, and then thrice at regular intervals on the arm with the highest blood pressure.

Carotid IMT Measurement

Guidelines and protocols of the Mannheim Consensus,[21] the American Heart Association (AHA),[22] and the Association of European Paediatric Cardiology[14] were followed to ensure standardized IMT measurement. The participants laid in supine position; head tilted at 45° to the opposite side of the scanned artery. The far wall of the right and left common carotid arteries were scanned longitudinally, at 1 cm from the end of the common carotid artery, during diastole. IMT was measured on a length of approximately 10 mm, twice on both the left and right sides. Operators measured IMT independently and were blinded to the participants' weight group.

B-Mode IMT Measurement Protocol

The semi-automatic B-mode IMT measurement was taken with the Toshiba AplioXG US machine (Toshiba, British Columbia, Canada) with a 12 zMHz frequency linear probe (18L7) and the measurement was analyzed using the M'Ath SR® software version 3.2.1 (Argenteuil, France). Operators drew a line, parallel to the intima-media interface, enabling the software to generate the semi-automated IMT measurement, aiming for a quality index >.5, and a variation between minimal and maximal values of IMT <.05 mm (Figure 1).

Radiofrequency Elastography and NIVE Based IMT Measurement Protocol

The IMT measurement was performed using uncompressed B-mode images obtained by computing the Hilbert transformation of radiofrequency signals. They were acquired on the same segment as for the B-mode IMT with an Ultrasonix SonixTouch scanner (Barnaby, BC, Canada) and a 14 MHz linear probe (L14-5/38), or a Terason uSmart 3300 (Burlington, MA, USA) and a 15 MHz linear probe (15L4A, S/N: 20696) using a video of at least 5 cardiac cycles. Parameters were comparable to B-mode IMT: depth of 3 or 4 cm, single focal zone, frame rate between 37 and 49 per second, dynamic range of 64 and focal range of 3 (Figure 2). The videos were analyzed with NIVE at the Laboratory of Biorheology and Medical Ultrasonics (LBUM) of the Montreal University Hospital Center (CHUM). A region of interest delineated by 2 contours defining the IMT was manually traced on a single frame of the cine-loop acquisition by the operators using a manual segmentation software. The traced contours were automatically tracked and propagated to all remaining frames using the likelihood of a Bayesian segmentation model.[23,24] NIVE uses the Nakagami speckle statistics inside the manually traced contours on a single frame to track the following frames of the video sequence.[23] The final IMT and elastography values reflect the mean over the entire frames (during diastole for IMT). Vascular elastography was assessed within the segmented IMT using the same radiofrequency-based videos for CAS, CLT, CAT and C|ShS| computations (Figure 3). Segmentation and NIVE techniques were implemented in C++ and Matlab R2018a.

Statistical Analysis

Statistical analysis was performed with IBM® SPSS® Statistics (Version 27.1.0.1) software. Comparison of the participant's clinical characteristics, mean IMT, ratio of mean IMT/diameter, and elastography parameters between weight groups was done using a student *t*-test for independent samples or Mann–Whitney *U* test for skewed data. Normality of distribution was assessed beforehand with the Shapiro–Wilk test. We considered $P < .05$ as statistically significant. An ANOVA was performed to compare the right and left carotid measurements. Then, a scale analysis of reliability and validity (ICC) was calculated for the 2 measurement techniques individually, and reliability between the 2 techniques was measured. ICC estimates and their 95% confidence intervals (CI) were calculated based on mean-rating, absolute agreement, two-way random effects model (3,k).[25] An ICC of less than .5 indicated poor reliability, between .5 and .75 moderate reliability, between .75 and .90 good reliability and >.90 excellent reliability for clinical applications.[26] Pearson analysis assessed the correlation between the technician's years of experience and mean intra-operator ICC, and the correlation between both techniques. The intraclass coefficient of variation was also calculated for each operator and averaged for each measurement technique, aiming for the American Society of Echocardiography Carotid Intima-Media Thickness's

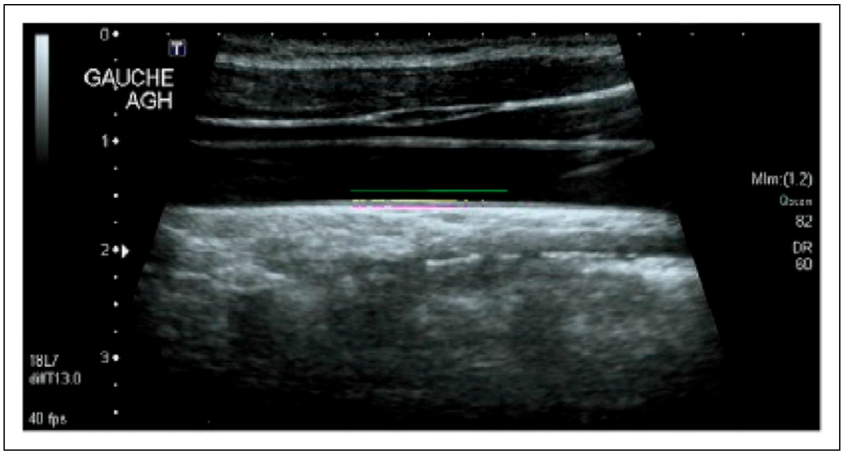

Figure 1. Example of semi-automatic common-carotid B-mode based IMT measurement taken on Math'SR software on a 10-year-old girl. A parallel green line is drawn in the lumen of the artery, indicating to the software where to take the measurement. The software gives the minimum, mean and maximum IMT, standard deviation and quality index of the measurement. Quality index indicates the percentage of measurements taken by the software for the calculation of IMT, between the yellow and pink lines. We aimed for a .5 quality index.

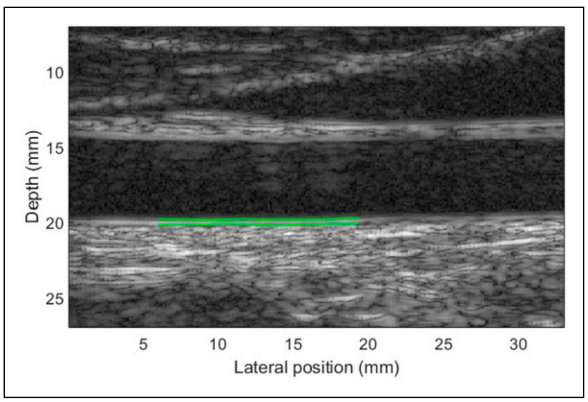

Figure 2. Example of the automatic step in common carotid IMT measurement taken from NIVE segmentation on a 10-year-old girl. Intima-media interfaces from a single frame are manually drawn by the operator. Subsequently, a mathematical and statistical algorithm automatically tracks this interface on the remaining frames of the sequence (at least 280 frames). To calculate IMT, the centre line between both interfaces is first computed. The IMT is defined as the average length of the segments that are passing through each point of the center line, joining both interfaces and being perpendicular to the center line. The images are then analysed with the NIVE software to measure vascular elastography components.

benchmark of a 6% coefficient of variation between operators.[27]

Results

Participant Characteristics

One hundred and thirty-three children were assessed for eligibility, 121 were contacted, 52 accepted and 30 were analyzed (Figure 4). Out of the 30 participants analyzsed, 12 had a BMI above the 85th percentile for age and sex, therefore considered as overweight or obese, and 18 were under, considered as normal weight. Seventeen (56.7%) were girls and thirteen (43.3%) were boys. Two IMT measurements for each of the right and left common carotid arteries were taken by each of the 6 operators for all the 30 participants, for a total of 720 measurements for each imaging outcome. The operators (EA, REJ, AG, CL, BK and RM) had different years of experience: 1, 11, 6, 12, 5 and 12 years, respectively. The overweight/obese group had significantly higher waist ($P < .001$) and calf ($P < .001$) circumferences, as well as tricipital ($P < .001$), subscapular ($P < .001$) and supra-iliac ($P < .001$) skinfolds. Systolic ($P = .001$) and pulse ($P = .003$) pressures were significantly higher in the overweight/obese group as well as mean B-mode IMT/mean diameter ($P = .035$). There was no difference in diastolic blood pressures ($P = .067$). There was no significant difference in IMT between the normal vs overweight/obese children: B-mode (.47 ± .08 mm and .51 ± .07 mm, respectively ($P = .15$)) and NIVE-based IMT (.45 ± .07 mm and .44 ± .05 mm, respectively ($P = .60$). There was also no significant difference between the 2 groups for diameter ($P = .98$), for the mean NIVE-based IMT/mean diameter ratio ($P = .50$), and the NIVE parameters CAS ($P = .072$), CLT ($P = .52$), CAT ($P = .097$) and C|ShS| ($P = .85$) (Table 1).

Comparability of the Right and Left Carotid Arteries

We found no statistically significant difference in mean IMT between the right and left carotids for B-mode ($P = .57$) and NIVE-based IMT ($P = .70$) analyses, and similarly for CAS ($P = .52$), CAT ($P = .67$), CLT ($P = .92$) and C|ShS| ($P = .28$). ANOVA also did not show a statistically significant difference in all 4 measurements (2 measurements by side) for each operator: B-mode ($P = .60$-.97), NIVE-based IMT ($P = .63$-.97), CAT ($P = .72$-.99), CLT ($P = .87$-.99), CAS ($P = .26$-.95) and C|ShS| ($P = .34$-.73). This comparability between sides

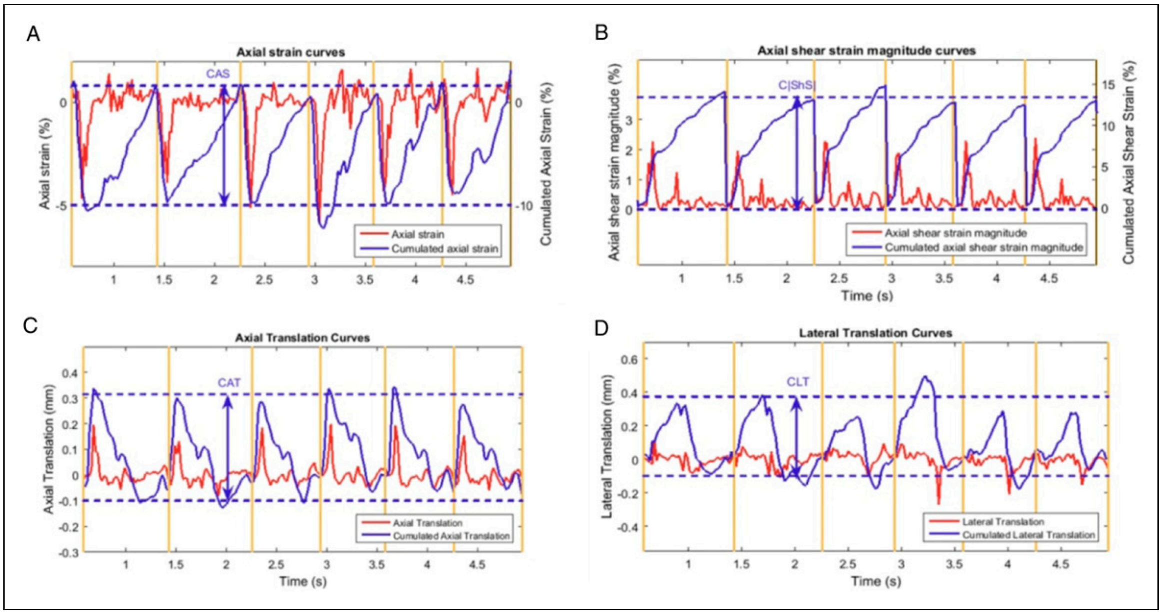

Figure 3. Time-varying NIVE curves on a 10-year-old girl. Elastography parameters of cumulated axial strain (CAS) (A), cumulated axial shear strain magnitude (C|ShS|) (B) and cumulated axial (CAT) (C) and lateral (CLT) (D) translations are represented by blue arrows. Axial strain, axial shear strain magnitude and axial and lateral translations are represented by red curves; corresponding cumulated curves are displayed in blue. Cardiac cycles are delimited by yellow lines.

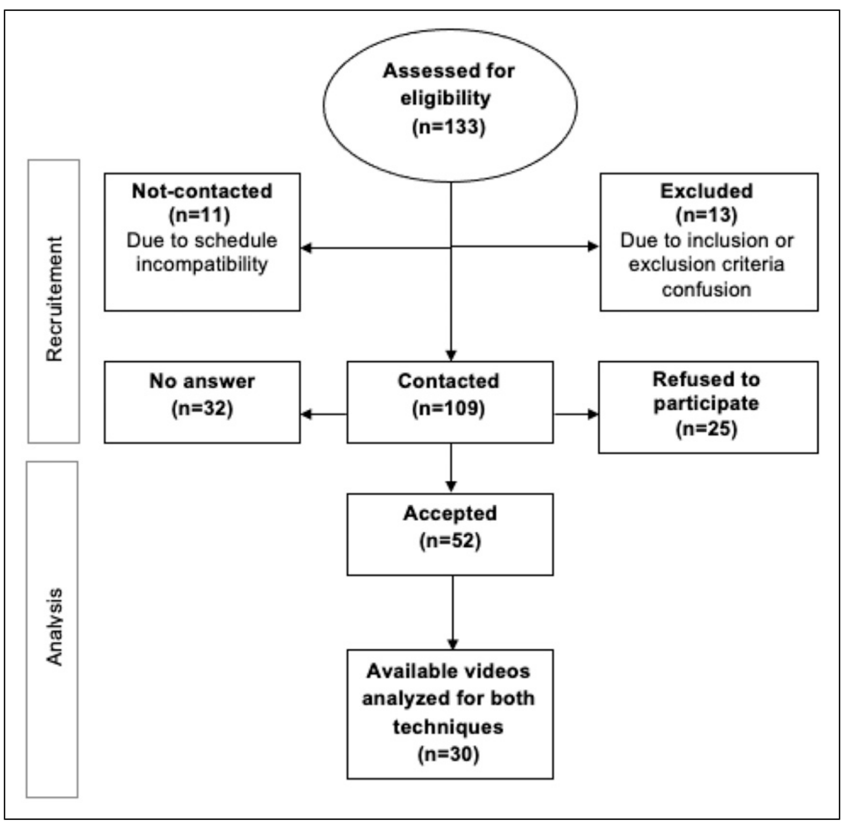

Figure 4. Flow chart of study participants.

Table 1. Clinical Characteristics of the Study Population, IMT and Elastography Measurements According to Weight.

Variable	Normal weight (n = 18) Mean ± SD	Overweight or obese (n = 12) Mean ± SD	Significance *P*-value
Age* (years)	12.65 ± 1.11	13.59 ± 1.29	.06
BMI* (kg/m^2)	17.98 ± 1.99	32.19 ± 7.78	<.001
Waist circumference* (cm)	62.95 ± 4.99	95.26 ± 22.13	<.001
Calf circumference (cm)	29.43 ± 3.21	38.85 ± 3.78	<.001
Triceps skinfold (mm)	17.80 ± 4.22	33.25 ± 8.31	<.001
Subscapular skinfold* (mm)	10.41 ± 4.32	30.58 ± 12.11	<.001
Supra-iliac skinfold* (mm)	13.02 ± 4.45	38.76 ± 10.59	<.001
Systolic blood pressure (mmHg)	105.31 ± 7.52	118.01 ± 10.23	.001
Diastolic blood pressure (mmHg)	61.70 ± 6.12	66.74 ± 8.39	.067
Pulse pressure (mmHg)	43.61 ± 5.89	51.28 ± 7.17	.003
Carotid Diameter (mm)	4.52 ± .86	4.51 ± .66	.98
Mean IMT B-mode (mm)	.47 ± .08	.51 ± .07	.15
Ratio: Mean IMT B-mode/Mean diameter	.106 ± .012	.115 ± .008	.031
Mean IMT NIVE (mm)	.45 ± .07	.44 ± .05	.60
Ratio: Mean IMT NIVE/Mean diameter	.103 ± .022	.099 ± .012	.50
Mean CAS (%)	11.97 ± 2.6	10.29 ± 2.03	.072
Mean CAT (mm)	.60 ± .19	.52 ± .15	.097
Mean CLT* (mm)	.64 ± .53	.61 ± .51	.52
Mean C|ShS|* (%)	6.09 ± 1.71	5.92 ± 1.60	.85

Independent student *t*-tests *P*-value; *age, BMI, waist circumference, subscapular skinfold, supra-iliac skinfold, mean CLT and mean C|ShS| were not normally distributed, therefore *P*-values were calculated with a Mann–Whitney *U* test. BMI: Body Mass Index, IMT: Intima-Media Thickness, NIVE: Non-Invasive Vascular Elastography, CAS: Cumulated axial strain, CAT: Cumulated axial translation, CLT: Cumulated lateral translation, C|ShS|: Cumulated axial shear strain magnitude.

was useful, as the data for each side was averaged into 1 mean value for each participant.

Reliability of B-Mode and NIVE-Based IMT Measurements

Inter-operator ICC was calculated for all operators assessing reliability between both IMT measurement techniques. The inter-operator ICC between both techniques was .30 [95% CI: −.31; .65]. Pearson correlation between IMT techniques was not significant (r = .21, *P* = .26). However, Bland-Altman graph shows agreement between both techniques. (Figure 5).

Inter-operator ICC for mean B-mode IMT between the 6 operators was .98 [95% CI: .97; .99]. The intra-operator ICC and their 95% CI for the 6 operators were .93 [.87; .96], .92 [.87; .96], .93 [.87; .96], .90 [.83; .95], .91 [.85; .95] and .91 [.84; .96], respectively. The average coefficient of variation was 3.93%.

Inter-operator ICC for mean NIVE-based IMT between the 6 operators was .70 [95% CI: .47; .85]. The intra-operator ICC and their 95% CI for the 6 operators were .78 [.6; .89], .80 [.64; .90], .71 [.48; .85], .94 [.90; .97], .81 [.67; .90] and .90 [.82; .94], respectively. The average coefficient of variation was 18.5%.

Inter-operator ICC for the parameter IMT/diameter ratio, assessing the reliability of the ratio of B-mode IMT/diameter with NIVE-IMT/diameter was: .37 [95% CI: −.22; .69] and when we looked at the overweight subgroup alone: .36 [95% CI: −.27; .77].

Reliability of NIVE-Based Elastography Parameters

Inter-operator ICC and 95% CI were calculated for each elastography parameter CAS .96 [.93; .98], CAT .99 [.99; 1.00], CLT .99 [.99; 1.00] and C|ShS| .98 [.97; .99]. Intra-operator ICC was also calculated for each elastography parameter for the 6 operators. For CAS, the lowest to highest ICC [95% CI] varied between .34 [−.18; .66] and .66 [.37; .83], CAT .61 [.28; .81] and .72 [.51; .86], CLT .94 [.89; .97] and .95 [.90; .97] and for C|ShS| .28 [−.30; .64] and .58 [.26; .79].

Reliability of B-Mode IMT, NIVE-Based IMT and NIVE-Based Elastography Parameters Based on Subgroup

Inter and intra-operator ICC were calculated for each weight subgroup as listed in Table 2 and Table 3 and reported with their 95% CI.

Correlation With Respect to Operator Experience

No significant correlation was seen for the relationship between operator experience in years and reliability of measurements (*r* = .69, *P* = .12).

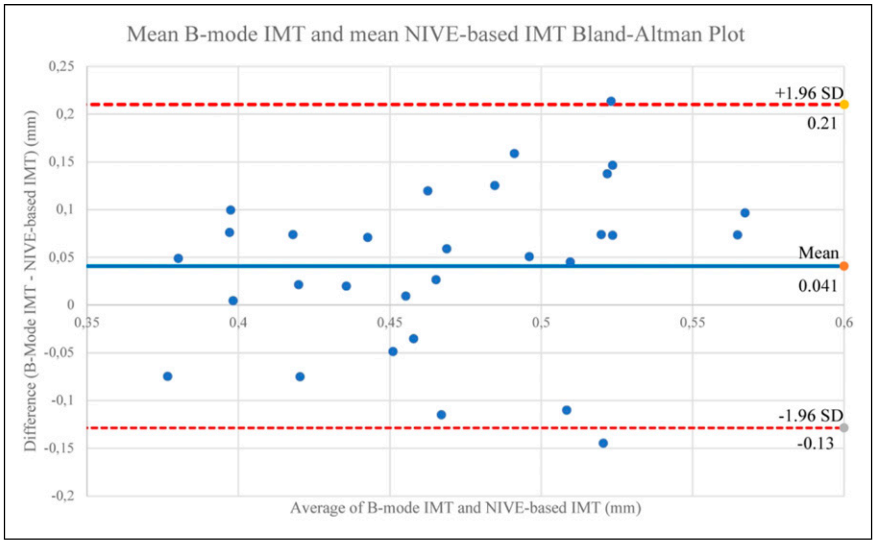

Figure 5. Mean B-mode and mean NIVE-based IMT Bland-Altman Plot. Bland-Altman plot showing the relationship between the B-mode automated technique and NIVE based IMT technique, which depends on an initial manual segmentation. Most values are different from zero and the difference is positive indicating higher values for the B mode based IMT measurements. The plot shows acceptable agreement between the 2 techniques, as only 2 out of 30 (6.67%) of the points lie outside of the 95% limits, and the limit of agreement between techniques is of 17%. To note however that the clinically significant limits are to be determined in children.

Discussion

We aimed to validate IMT measurements with B-mode and NIVE-based IMT as subclinical markers for atherosclerosis in children. Inter- and intra-operator ICCs were of moderate to excellent reliability between the 6 operators for the B-mode and NIVE-based techniques. There was poor reliability between the 2 techniques when assessing IMT, and IMT/diameter ratio independently of the subgroup. Inter-operator ICC was excellent for all elastography parameters, but intra-operator ICCs ranged from poor to excellent. Subgroup analysis gave the same results. In addition, knowing that the IMT/diameter ratio considers body habitus, which can affect IMT measurement,[10] we found an increased ratio in the overweight subgroup, using B-mode IMT. This is in keeping with the physiologic haemodynamic response to increased body habitus. We lack statistical power to obtain a lower ratio in overweight and obese children when IMT exceeds a threshold, as stated in the literature.[10] The purpose of the current study is not to compare weight subgroups, which will be the objective of our future studies.

The difference in reliability between inter and intra-operator ICC for NIVE-based IMT and elastography parameters is explained by the use of 4 IMT values to calculate intra-operator ICC, but only the mean value to calculate inter-operator ICC. We suggest that IMT and elastography measurements in children be repeated and averaged.

Operators were the same for both techniques. Operator experience varied between 1 and 12 years. A high correlation, though not significant, between experience and intra-operator reliability was obtained. A bigger sample size could give different results.

Table 2. Inter-operator ICC based on subgroup.

Parameter	Normal weight [95% CI]	Overweight [95% CI]
B-mode IMT	.99 [.97; .99]	.98 [.94; .99]
NIVE-based IMT	.75 [.50; .89]	.62 [.24; .86]
CAS	.96 [.93; .98]	.95 [.88; .98]
CAT	.99 [.99; 1.00]	.99 [.98; .99]
CLT	.99 [.99; 1.00]	.99 [.99; 1.00]
SHS	.98 [.96; .99]	.97 [.97; .99]

ICC: Inter-class correlation, NIVE: Non-Invasive Vascular Elastography, CAS: Cumulated axial strain, CAT: Cumulated axial translation, CLT: Cumulated lateral translation, C|ShS|: Cumulated axial shear strain magnitude, CI: Confidence Interval.

In adults, multiple studies have shown that automatic measurements usually have better reproducibility and lower variability compared to manual measurements, as it is illustrated in our study with a low coefficient of variation (3.93%) for the semi-automatic B-mode technique.[28,29] Dogan et al.[30] found a poor correlation between manual and automated techniques. In fact, the precision of a manual system on a radiological screen for one pixel is of .2 mm, therefore, for a 10 mm segment, accuracy is of 9%.[31] This seems inadequate for the inherently smaller vascular wall thickness in children; therefore, semi-automated techniques could be more accurate. Nevertheless, the semi-automatic B-mode technique relies on the post-processing performed by the commercial ultrasound machine, that is, images are filtered and compressed in amplitude. NIVE on the other hand uses raw ultrasound data to compute its own B-mode

Table 3. Intra-operator ICC based on subgroup.

Parameter	Normal weight [95% CI]	Overweight [95% CI]
B-mode IMT	.93-.95 [.86; .95-.91; .98]	.82-.90 [.56; .94-.76; .97]
NIVE-based IMT	.69-.97 [.37; .88-.94; .99]	.37-.89 [-.68; .81-.74; .95]
CAS	.27-.70 [-.51; .70-.37; .88]	.22-.64 [-1.46; .81-.11; .89]
CAT	.55-.69 [.03; .82-.33; .88]	.72-.80 [.21; .93-.51; .94]
CLT	.96-.97 [.92-.99; .94-.99]	.88-.92 [.71-.97; .79-.98]
SHS	.21-.58 [-.79-.70; .069-.84]	.01-.67 [-1.46-.70; .15-.91]

images and is consequently more precise. This explains the excellent inter-operator ICC for all elastography parameters.[32] However, the NIVE technique uses a manual and operator-dependent first step of segmentation, which can add heterogeneity between operators, especially when there is poor lumen-intima and media-adventitia interface delineation. It is illustrated in this study with a high coefficient of variation (18.5%) for this technique.[27] Nevertheless, speckle statistics should robustly adjust the automatic propagation of the contour on subsequent frames of the video. These limitations, inherent to each technique, explain the poor correlation between techniques in our study. This confirms the necessity of having technique-specific reference tables when screening children with IMT.

Most of the literature in children compared B-mode and radiofrequency IMT techniques, which correlate well in adults.[33] This is not the case in children, nor do B-mode and NIVE-based IMT correlate in children, as illustrated by poor ICC and Pearson correlation.[9] It reflects the poor ability of the techniques to calculate the same measurement despite measurement error or operator-variability.[34] But, the Bland-Altman plot shows good agreement, and that closeness of the measurements obtained by the different techniques is somewhat acceptable.[34] However, we do not know the 5th and 95th percentile of normal technique specific IMT values in children yet. Further studies are needed.

Our study has some limitations. A selection bias could possibly be introduced when considering the recruitment of participants despite strict inclusion and exclusion criteria. Some of the radiofrequency exams were performed using an old Ultrasonix system, and others using the Terason3300 scanner, both using different transducers and frequencies, which could affect axial and lateral resolutions, and limit the comparability of parameters. Despite this fact, the inter- and intra-operator reliability ranged from poor to excellent. Finally, the sample size is small and does not have enough power to compare IMT between subgroups. Knowing that it is not the main objective of this paper, the use of IMT in this study was for early atherosclerosis-detection in normal weight and overweight children. Underweight children were not represented and results could differ for this weight group.

In conclusion, IMT assessment in children is reproducible using B-mode ultrasound or NIVE-based IMT using speckle statistics. However, the two techniques correlate poorly and could not be interchangeable in the absence of the lower and higher clinical limits of IMT values. The same technique should be used for the time being. NIVE-based IMT speckle statistics technique depends on an initial manual segmentation, explaining the higher coefficient of variation between operators. However, the automated subsequent analysis gives the advantage of calculating IMT and vascular elastography parameters based on a powerful mathematical and statistical approach. Further studies are needed to obtain normative IMT charts using both techniques and for elastography. These charts should be integrated in clinical decision algorithms for risk stratification of atherosclerosis in children.[35] On the other hand, if IMT is increased, clinicians should search for undiagnosed risk factors, such as diabetes, hypertension and hypercholesterolaemia in children.[35]

Appendix

Abbreviations

BMI	Body Mass Index
ICC	Intra-class correlation coefficient
IMT	Intima Media Thickness
NIVE	Non-Invasive Vascular Elastography

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