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Sundholm, Johnny

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Semi-automatic border detection software for the quantification of arterial lumen, intima-media and adventitia layer thickness with very-high resolution ultrasound

Johnny Sundholm [a], Tomas Gustavsson [b], Taisto Sarkola [a,*]

[a] Children's Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
[b] Chalmers University of Technology, Gothenburg, Sweden

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ABSTRACT

Background: The aim was to evaluate the accuracy, precision and feasibility of semi-automatic border detection software (AMS) in comparison to manual electronic calipers (EC) in the analysis of arterial images obtained with transcutaneous very-high resolution vascular ultrasound (VHRU, 25–55 MHz).
Methods: 100 images from central elastic and peripheral muscular arteries were obtained on two separate imaging occasions from 10 healthy subjects, and independently measured with AMS and EC.
Results: No bias between AMS and EC was found. The intraobserver coefficients of variation (CV) for carotid lumen dimension (mean dimension 5.60 mm) was lower with AMS compared with EC (0.4 vs. 1.9%, $p = 0.033$; $N = 20$). No consistently significant differences in intra, inter or test-retest CVs were observed overall for muscular artery dimensions between AMS and EC. The intra CV for adventitial thickness (AT, mean 0.111 mm; 15.6 vs 24.8%, $p = 0.011$; $N = 41$) and inter CV for intima-media thickness (IMT, mean 0.219 mm; 14.3 vs. 21.2%, $p = 0.001$; $N = 58$) obtained with AMS in higher quality thin muscular artery images was lower compared with EC. The mean reading time was significantly lower with AMS compared with EC (71.5 s vs. 156.6 s, $p < 0.001$).
Conclusion: AMS is accurate, precise, and feasible in the analysis of arterial images obtained with VHRU. Minor, although statistically significant, differences in the precision of AMS and EC-systems were found. The precision of AMS was superior for AT and IMT in higher quality images likely related to a decrease in the technical variability imposed by the observer.

1. Introduction

Vascular sonography has long been used as a diagnostic tool for vascular diseases and in particular in the non-invasive assessment of atherosclerosis. The assessment of the carotid intima-media thickness (IMT) with conventional B-mode high resolution ultrasound (<15 MHz, HRU) is based on the recognition of the double line pattern in the image as originally validated by Pignoli et al. [1]. Automatic or semi-automatic border detection softwares have been developed to make analysis of the ultrasound image simpler, improve measurement precision, avoid drifts over time, and to make it less reliant on human operators overall compared with manual electronic calipers (EC) [2–9]. Hence, these softwares are now commercially available and recommended in recent international guidelines [9–11].

The use of transcutaneous very-high resolution ultrasound (VHRU, 25–55 MHz) has recently been developed [12,13] and provides, in contrast to HRU, the opportunity to accurately and precisely assess superficial and more peripheral muscular arteries in humans overall as well as central elastic arteries during infancy and childhood [14,15]. The increased axial resolution of VHRU (i.e. 0.04–0.05 mm with 55 MHz) also provides simultaneous assessment of intima-media and adventitial (AT) thicknesses, i.e. intima-media-adventitia thickness (IMAT) or the complete arterial wall of the muscular artery. This assessment is based on the recognition of the triple line pattern in the image [13]. We have also shown that the accuracy of the ultrasound derived arterial layer thickness measurement is related to ultrasound frequency when studying small arteries with a wall layer thickness in the 0.2–0.5 mm range [13,15]. Even if the resolution of VHRU is superior to HRU, the AT and IMT of small arteries are, nevertheless, close to the limit of

* Corresponding author. Children's Hospital, University of Helsinki and Helsinki University Central Hospital, POB 281, 00029 HUS, Helsinki, Finland. Tel.: +358 407030394; fax: +358 947174706.
E-mail address: taisto.sarkola@helsinki.fi (T. Sarkola).

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resolution, and inevitably challenged by a higher technical variability using laborious ECs.

A major benefit of using border detection softwares is a potential reduction in the variability of the measurement relating to differences in reading behavior over time or differences between different operators. As semi-automated border detection software may be considered as a single standard operator the inevitable variability imposed by human operators could potentially be minimized. Performing the measurement over a distance would also incorporate a larger area of assessment as well as speed up the analysis process of calculating the mean of multiple ECs. Increasing the precision of the measurement would obviously decrease the sample size needed to detect associations with cardiovascular risk factors or differences in arterial layer thickness over time within and/or between groups. Furthermore, the use of border detection software in VHRU image analysis including the simultaneous assessment of multiple arterial layers has not, to the best of our knowledge, been previously evaluated. We, therefore, intended to confirm the accuracy and hypothesize that we would be able to increase the precision of the VHRU image analysis and make it more feasible by incorporating a semi-automatic border detection software in the process.

The objective was to compare the accuracy, precision and feasibility of semi-automatic border detection software with ECs in VHRU image analysis. The research question was to elucidate whether the quantification of AT and IMT with VHRU would be more precise and feasible using a semi-automatic border detection software compared with manual ECs.

2. Materials and methods

100 images from 10 healthy subjects of both sexes including both adults and children (age range 5–56 years) were obtained at two occasions two weeks apart by a single operator. Images of the common carotid artery (CCA) and different muscular arteries (brachial, BA; femoral, FA; tibial, TA, and radial, RA) were obtained bilaterally with VHRU (Vevo 770, Visualsonics, Toronto) using 25 MHz (RMV710B), 35 MHz (RMV712) and 55 MHz (RMV708) transducer frequencies. The resolution for each of the transducers was 0.0156 mm/pixel for 55 MHz, 0.0196 mm/pixel for 35 MHz, and 0.0357 mm/pixel for the 25 MHz transducer. The CCA was imaged 1 cm proximal to the bulb, BA 2 cm proximal to the cubital skin fold, FA at the inguinal skin fold, TA at the medial malleolar level, and RA 1 cm proximal to the palma manus. Image clips including 300 frames with a frame rate of 40 frames per second were obtained. Gain settings were optimized in order to minimize the amount of scatter and produce a sharp distinction between the different wall layers. The double line (CCA) and triple line (BA, FA, TA and RA) patterns were ascertained and care taken not to compress the arteries during image acquisition. The quality of images were subjectively graded as 0, 1, 2 or 3, with 0 designated as an unreadable clip, 1 as poor image quality including poor distinction of far wall layers, 2 as fair image quality images with all lines at least partially visible, and 3 as excellent image quality including excellent distinction of far wall layers.

Lumen dimension (LD) was defined as the distance from leading edge of near wall lumen-intima interface to the leading edge of far wall lumen-intima interface, IMT as the distance from leading edge of far-wall lumen-intima interface (first line) to leading edge of far-wall media-adventitia interface (second line), and intima-media-adventitia thickness (IMAT) as the distance from leading edge of far-wall lumen-intima interface (first line) to the leading edge of the adventitia-perivascular fat interface (third line). Adventitia thickness (AT) was calculated as the difference between IMT and IMAT (Fig. 1).

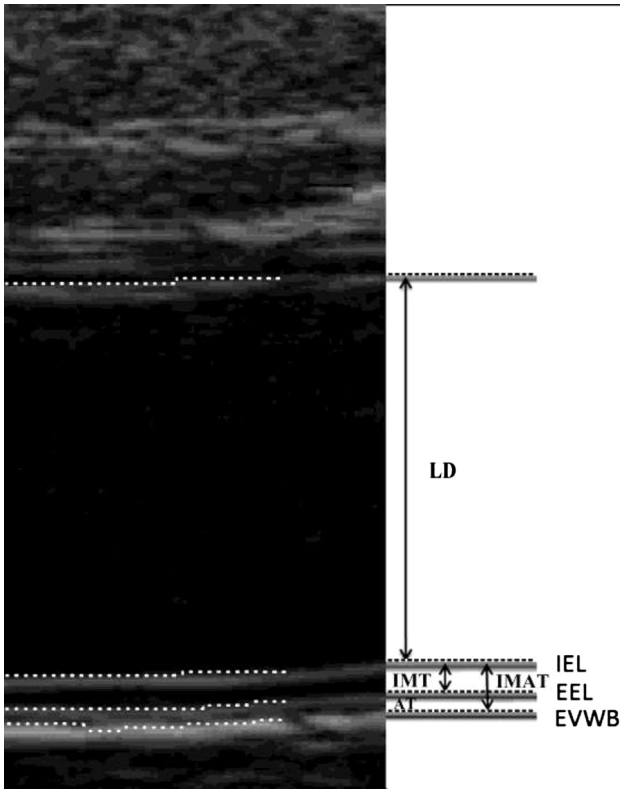

Fig. 1. VHRU image of the brachial artery with software border detection lines and a schematic image of the different layers in the three-line pattern of muscular arteries. LD = lumen dimension, IMT = intima-media thickness, IMAT = intima-media-adventitia thickness, AT = adventitia thickness, IEL = internal elastic lamina, EEL = external elastic lamina, EVWB = extravascular wall border.

A still image at end-diastole ascertained with simultaneously recorded electrocardiogram was chosen from the clip and independently analyzed off-line using both the Vevo 770 software (version 3.0.0) system with manual ECs and a semi-automatic border detection software (AMS, Arterial Measurement System [3], gustav@alumni.chalmers.se). The mean of three EC measurements were used in the final analyses.

The image was converted to TIFF-format in Vevo 770 prior to analysis with AMS, thus speeding up the analyzing process without loss of quality. AMS was unable to read higher resolution images with appropriate calibration, therefore a 26.8 pixel/mm calibration was used to analyze images and the measurement converted into millimeters using each frequency's own calibration with the following formula:

$$X_R = X_{AMS} \times \frac{C_{AMS}}{C_f}$$

where X_R is the measurement in millimeters, X_{AMS} is the result given by AMS, C_{AMS} is the calibration (pixel/mm) used in AMS, and C_f the calibration for transducer frequency (25 MHz = 28.4 pixel/mm, 35 MHz = 51.2 pixel/mm and 55 MHz = 64 pixel/mm). A standard 1–2 cm wide region of interest in the area of best far wall image quality was selected by the operator. The borders for LD, IMT, and IMAT were then automatically traced and measured by the software, and care taken not to adjust the detection lines unless deemed necessary by the operator. The time to the closest second taken from image conversion of the clip to the measurement result was recorded in a subset of 20 images using both systems.

For intraobserver variability, the images obtained during the first occasion were independently analyzed two times (at least two

Table 1
Intraobserver agreement of AMS and EC for different transducer frequencies, arterial sites and dimensions.

Artery	Dimension	*N*	Mean thickness		Δ Mean (LOA 95%)		CV%		*p*-value
			AMS	EC	AMS	EC	AMS	EC	AMS vs EC
Carotid	LD	20	5.601	5.559	0.010 (−0.036, 0.056)	0.034 (−0.177, 0.240)	0.4	1.9	0.033
(25 MHz)	IMT	20	0.373	0.358	−0.006 (−0.072, 0.061)	−0.001 (−0.069, 0.067)	9.2	9.8	0.825
Femoral	LD	20	7.751	7.849	−0.018 (−0.425, 0.388)	−0.062 (−0.636, 0.513)	2.7	3.7	0.270
(25 MHz)	IMT	20	0.325	0.330	0.009 (−0.069, 0.087)	0.004 (−0.048, 0.055)	12.3	8.0	0.226
	IMAT	20	0.564	0.601	0.020 (−0.090, 0.130)	−0.025 (−0.189, 0.139)	10.0	14.0	0.397
	AT	20	0.239	0.271	0.010 (−0.083, 0.103)	−0.029 (−0.180, 0.123)	19.9	28.6	0.104
Brachial, Radial, Tibial	LD	56	2.505	2.480	−0.008 (−0.087, 0.070)	−0.002 (−0.067, 0.071)	1.6	1.4	0.826
(35–55 MHz)	IMT	59	0.182	0.179	0.007 (−0.021, 0.036)	0.001 (−0.030, 0.032)	8.0	8.8	0.597
	IMAT	58	0.291	0.285	0.003 (−0.036, 0.042)	0.003 (−0.044, 0.049)	6.8	8.3	0.197
	AT	60	0.108	0.106	−0.001 (−0.047, 0.045)	0.000 (−0.051, 0.051)	21.7	24.5	0.310

LD, lumen dimension; IMT, intima-media thickness; IMAT, intima-media-adventitia thickness; AT, adventitia thickness; CV, coefficient of variation; Δ Mean, mean difference; LOA 95%, 95% limits of agreement; AMS, semi-automatic border detection; EC, electronic calipers.

weeks apart) with both systems by a single operator. For the interobserver variability, a second operator analyzed these images independently with both systems. For test-retest variability (reproducibility), the first operator analyzed images from the second imaging occasion using both systems. Both operators were highly experienced.

2.1. Data analysis

Results are reported as mean with SD, median with minimum and maximum values, and ratios, as appropriate. Agreement was quantified by calculating the mean difference, 95% limits of agreement (LOA), and coefficient of variation (CV). A Bland–Altman plot [16] will be used to analyze the agreement for AMS. To statistically compare the technical variance imposed by the operator the mean difference was subtracted from the difference between each paired measurement and then converted into absolute value as follows:

$$\Delta x_{\mathrm{mi}} = |\Delta x_{\mathrm{i}} - \Delta\bar{x}|$$

where Δx_{mi} is the modified difference used for analysis Δx_{i}, is the difference for each measurement, and $\Delta^{\bar{x}}$ the mean difference for each group. Outliers defined as mean ± >3SD were excluded. Paired Student's *t*-test was used for statistical comparison between modified differences and $p < 0.05$ regarded as statistically significant.

To explore explanatory factors related to measurement precision a linear regression model was set up with CV as the dependent variable. The independent variables entered in the model were reliability, image quality, software, and dimension. Reliability was split into two separate variables, image and observer dependent reliability. The image dependent reliability divided the data into 1 = data in which the same image was analyzed twice (i.e. intra- and interobserver), and 2 = data in which two different images of the same artery were analyzed (i.e. test-retest). The observer dependent reliability divided the data into 1 = images analyzed twice by the same observer (i.e. intraobserver), and 2 = images analyzed by two different observers (i.e. interobserver). The image quality variable divided the data into 1 = lower quality images (quality grade 1–2) and 2 = higher quality images (quality grade 3). The software variable was given 1 = AMS and 2 = EC. Dimension was set as a scale variable using the logarithm of the measured distance in pixels, log(pixel), as an exponential relation between the CV and dimension was observed. Data was analyzed with SPSS for Windows (Version 18.0).

3. Results

No bias between EC and AMS measurements were observed (Tables 1–3). The precision for the different measurements with AMS and EC are displayed in Tables 1–3 and Fig. 2. The technical variability for the different arterial dimensions ranged from ± 30 μm 95%LOAs for muscular arterial IMT to ± 600 μm 95% LOAs for large arterial LDs. As expected, the largest CVs were observed for interobserver and test-retest variability of the thinnest adventitial dimension. Minor differences in intraobserver CVs between AMS and EC were observed for carotid LD (AMS 0.4 vs. EC 1.9%, $p = 0.033$), for test-retest femoral LD (AMS 8.9 vs. EC 7.3%, $p = 0.020$) and AT (AMS 23.4 vs. EC 37.4%, $p = 0.050$).

When assessing the precision of AMS measurements in relation to images quality (grade 1–2 vs. grade 3), a negative association between quality and CVs was observed (Supplementary Tables 4–6) In the subset of high quality images significant differences were found between AMS and EC for intraobserver AT (AMS 15.6 vs. EC 24.8 p = 0.011) and test- retest IMT (AMS 14.3 vs. EC 16.9,

Table 2
Interobserver agreement of AMS and EC for different transducer frequencies, arterial sites and dimensions.

Artery	Dimension	*N*	Mean thickness		Δ Mean (LOA 95%)		CV%		*p*-value
			AMS	EC	AMS	EC	AMS	EC	AMS vs EC
Carotid	LD	18	5.589	5.594	0.008 (−0.147, 0.163)	−0.030 (−0310, 0.249)	1.4	2.6	0.098
(25 MHz)	IMT	20	0.398	0.382	−0.049 (−0.164, 0.067)	−0.047 (−0.116, 0.022)	14.8	9.2	0.065
Femoral	LD	20	7.676	7.676	0.149 (−0.497, 0.795)	0.345 (−0.451, 1.140)	4.3	5.3	0.333
(25 MHz)	IMT	19	0.316	0.322	0.019 (−0.065, 0.103)	0.003 (−0.063, 0.069)	13.5	10.4	0.109
	IMAT	19	0.577	0.600	−0.027 (−0.172, 0.119)	−0.015 (−0.095, 0.064)	12.9	6.8	0.001
	AT	19	0.261	0.278	−0.035 (−0.169, 0.099)	−0.013 (−0.125, 0.098)	26.1	20.5	0.184
Brachial, Radial, Tibial	LD	56	2.500	2.485	0.004 (−0.146, 0.155)	−0.007 (−0.119, 0.105)	3.1	2.3	0.180
(35–55 MHz)	IMT	57	0.180	0.183	0.003 (−0.036, 0.042)	−0.004 (−0.034, 0.026)	11.2	8.5	0.159
	IMAT	58	0.291	0.286	0.003 (−0.053, 0.058)	−0.000 (−0.045, 0.045)	9.8	8.1	0.265
	AT	58	0.110	0.103	−0.003 (−0.051, 0.045)	0.005 (−0.031, 0.041)	22.3	17.9	0.267

See Table 1 for abbreviations.

Table 3
Test-retest agreement of AMS and EC for different transducer frequencies, arterial sites and dimensions.

Artery	Dimension	*N*	Mean thickness		Δ Mean (LOA 95%)		CV%		*p*-value
			AMS	EC	AMS	EC	AMS	EC	AMS vs EC
Carotid	LD	20	5.555	5.503	0.082 (−0.864, 0.700)	0.112 (−0.516, 0.740)	7.2	5.8	0.191
(25 MHz)	IMT	20	0.376	0.404	−0.008 (−0.108, 0.092)	−0.092 (−0.196, 0.013)	13.6	13.3	0.819
Femoral	LD	20	7.623	7.665	−0.255 (−1.588, 1.077)	0.367 (−0.724, 1.458)	8.9	7.3	0.020
(25 MHz)	IMT	20	0.325	0.327	0.001 (−0.113, 0.116)	0.005 (−0.117, 0.128)	18.0	19.1	0.905
	IMAT	20	0.576	0.618	−0.023 (−0.212, 0.165)	−0.034 (−0.292, 0.225)	16.7	21.4	0.045
	AT	20	0.251	0.291	−0.025 (−0.140, 0.091)	−0.039 (−0.252, 0.174)	23.4	37.4	0.050
Brachial, Radial, Tibial	LD	60	2.474	2.455	−0.040 (−0.536, 0.455)	0.048 (−0.378, 0.475)	10.2	8.9	0.101
(35–55 MHz)	IMT	60	0.183	0.183	0.002 (−0.055, 0.060)	−0.009 (−0.052, 0.035)	16.0	12.0	0.915
	IMAT	59	0.293	0.292	0.000 (−0.088, 0.088)	−0.015 (−0.095, 0.065)	15.3	9.8	0.290
	AT	60	0.110	0.109	−0.002 (−0.068, 0.063)	−0.007 (−0.078, 0.064)	30.3	33.3	0.644

See Table 1 for abbreviations.

$p = 0.044$). In the subset of low quality images significant differences were found for intraobserver LD (AMS 1.9 vs. EC 4.3, $p = 0.032$), test-retest LD (AMS 11.1 vs. EC 7.6, $p = 0.020$).

When the time to analyze 20 images with both EC and AMS was measured, the reading time for a single image with AMS was 71.5 ± 16.6 s. For EC the reading time for a single image was 156.6 ± 37.2 s. When comparing AMS with EC the reading time was significantly lower for AMS ($p < 0.001$).

In multiple regression analyses dimension was the strongest predictor of CV ($R^2 = 0.125$, $B = -4.800$, $p < 0.001$, note that the association is exponential). Other significant explanatory factors of precision were image dependent reliability ($R^2 = 0.025$, $B = 2.669$, $p < 0.001$), and image quality ($R^2 = 0.015$, $B = -2.446$, $p < 0.001$). Non-significant variables in the model were observer dependent reliability ($R^2 = 0.002$, $p = 0.169$) and software ($R^2 = 0.000$, $p = 0.450$). The R^2 of the whole model was 0.171.

4. Discussion

In the present study we compared the performance of semi-automatic border detection software (AMS) with electronic caliper (EC) measurements in the analysis of arterial images obtained with VHRU. The main findings were the following: The image processing time was significantly shorter using AMS. AMS is sufficiently accurate as we observed no bias compared to EC. In addition, AMS was precise and feasible and may then be used as an alternative to EC when measuring VHRU images obtained from central elastic and peripheral muscular arteries.

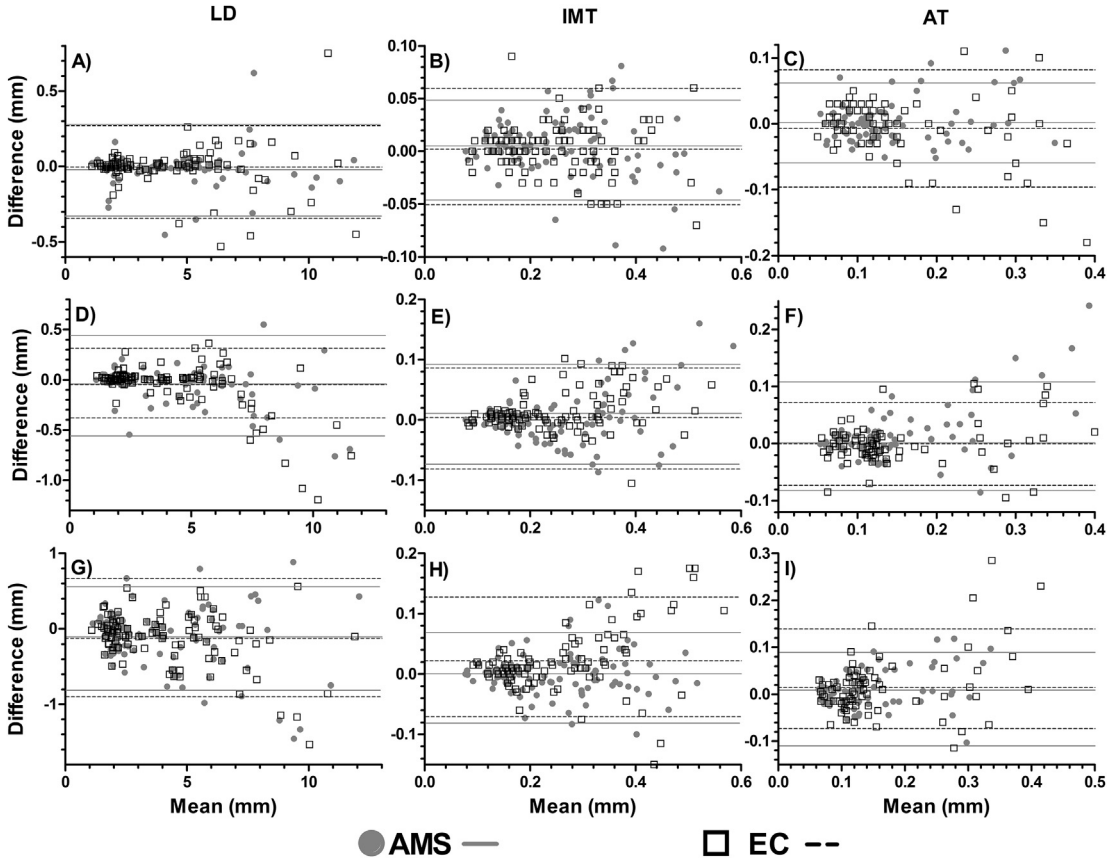

Fig. 2. Bland–Altman plots on AMS- and EC-derived intra (A–C), inter (D–F), and test-retest (G–I) agreements for lumen dimension (LD), intima-media thickness (IMT) and adventitia thickness (AT) measurements. Mean difference and 95% limits of agreement are displayed with lines for both systems.

As the regression analyses show, the technical variability of the measurement is mainly related to the size of measured structures and the quality of the image. This was predictable as the smallest structures measured were close to the axial ultrasound resolution of the transducers.

In contrast to our expectations, we were unable to show a significant impact of the different analysis methods on measurement precision when analyzing the dataset as a whole. A difference between methods was observed when comparing smaller datasets only. Nevertheless, the precision of AMS was superior for carotid LD likely due to carotid structures easily being detected by AMS. This is similar to the use of automated software to track radiofrequency signals in the assessment of the carotid wall [17]. Differences in favor of AMS was also observed for thin layers, such as intra-observer AT, seen in intra- and interobserver measurements as well as the precision for interobserver measurements of small muscular artery IMT and test-retest measurements of femoral AT likely related to a decrease in the technical variability imposed by the operator. The precision of AMS was also superior in AT and IMT in higher quality images likely related to a decrease in the amount of manual adjustments of the detection lines deemed necessary by the operator in the analysis process. However, when analyzing difficult to read images of lower quality with AMS, such as femoral AT, the automatic border detection finds and traces the borders poorly. The decreased performance of AMS compared to EC in analyzing low quality images is likely depending on the increased manual interference needed and the reader being misled by the poor judgment of the automatic border detection software. The lack of a benefit of border detection software is in line with recent studies assessing the common carotid artery far wall IMT in healthy populations [18,19].

The time in image processing is an important feature of method feasibility as studies on cardiovascular risk typically involve large sample sizes and repeat assessments. In the present study the analysis time was far shorter when semi-automatic border detection was applied. This is likely due to AMS automatically tracing the vascular structures and instantly providing a value for the different dimensions whereas with EC each dimension is averaged from several separate manual measurements.

The study includes a number of limitations that has to be acknowledged. The results may only be applied to VHRU-images on healthy subjects without clinical signs of atherosclerosis. The age span of the test group did not include infants or patients with cardiovascular diseases. No plaques were observed among the study subjects and the present study provide no information relating to method performance to detect associations between layer thickness, cardiovascular risk factors, rates of change, or treatment effects. This was, however, not the objective of the study and we believe that our results may well be generalized to the pediatric population with small arterial structures, good imaging windows and no clinical atherosclerosis present. The limited number of study subjects also precludes comparison between different age groups. We nevertheless included different arterial sites and structures, multiple dimensions as well as a relatively large amount of images in order to assess the independent impact of different factors on precision overall. On the other hand we agree that the present sample size may still have failed to detect minor differences between the methods.

In conclusion, the use of semi-automatic border detection software is feasible, accurate and precise when analyzing VHRU images and may be used as an alternative to ECs. The precision of the software seems to be similar to manual ECs, but likely to be of benefit when analyzing images of good quality and with relatively normal arterial walls, in studies with large amounts of images involving multiple operators, and in settings involving the assessment of arterial wall thickness changes over time. The standardized tracking of the software may, thus, provide the ability to improve quality control and quality assurance of the measurements in clinical trials and large epidemiological studies.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2014.03.006.

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