Accuracy and Precision of Ultrasound Manual Measurement of Carotid Intima-media Thickness having Semiautomatic Method as Reference

Maristela Magnavita Oliveira Garcia, Ana Marice Teixeira Ladeia, Isis Vasconcelos Lima, Carolina Garcez Varela, Patricia Fontes da Costa Silva, Marilia Galeffi Rodrigues, Maria de Lourdes Lima Silva, Armênio Costa Guimarães, Luis Claudio Lemos Correia

Escola Bahiana de Medicina e Saúde Pública (EBMSP) - Fundação Bahiana para Desenvolvimento das Ciências (FDBC), Salvador, BA - Brazil

Abstract

Background: **The semiautomated ultrasound border detection technology for measurement carotid intimo-medio thickness (CIMT) provides shorter time of exam and minimal variability measures.**

Objective: **To evaluate the accuracy of the manual method, taking the semiautomated as reference and the reproducibility of the methods.**

Methods: **Data were obtained from women of Ambulatory of Obesity directed to CIMT measurements determination. The evaluation of the manual method (manualCIMT) was performed, taking the maximum thickness of the semiautomated method (samaxCIMT) as reference. The statistical analyses used Pearson correlation, degree of agreement and inter and intraobserver variabilities in the two models and Kappa test.**

Results: **In the sample of 59 women, there was a strong correlation of manualCIMT with samaxCIMT ($r = 0.84$, $p < 0.0001$) and a good agreement between both methods, given the small mean difference of measures (0.06 ± 0.04 mm), with limits of agreement at 95% level between -0.02 to 0.14 mm. The agreement on the definition of subclinical atherosclerosis was moderate, 53% (kappa 52%, $p < 0.0001$). The correlation between manual and semiautomated measurements in intra and inter-observer analyses was strong. The intraobserver reproducibility for manualCIMT measures was good and similar of interobserver, with a mean difference of 0.04 ± 0.03 mm and limits of agreement at 95% level between -0.02 to 0.10 mm. For CIMT similar result was observed.**

Conclusion: **The manual method of measuring carotid intima-media thickness could be validated as an alternative method to semiautomated.**

Keywords: **Carotid Intima-Media Thickness; Ultrasonography; Atherosclerosis; Benchmarking.**

Introduction

The Carotid Intima-Media Thickness (CIMT) has an independent association with cardiovascular risk factors, with atherosclerotic burden in different arterial sites, coronary events and strokes. The progression of CIMT can also be attenuated or reversed by intervention measures on risk factors.

The measurement of the carotid intima-media thickness has been used as surrogate endpoint of cardiovascular events in clinical trials for its association with risk factors for coronary artery disease and cardiovascular events.

The first morphological changes of CIMT can be viewed by two-dimensional ultrasound, non-invasively and with high image resolution. The new semiautomated measurement technology of CIMT was merged intending to reduce exam time and variability of measures, assigned to the manual method. Because of the mechanism of automatic edge detection, the modality adds advantage, especially for non-experienced examiners because the program facilitates the performance of the measures, with less operator influence, without compromising accuracy. However, it is quite costly and not available in all ultrasound laboratories.

Thus, the present study aimed at testing the accuracy of the manual method, taking as a reference the semiautomated. In addition, the reproducibility of the method was evaluated.

Mail: Luis C. L. Correia, MD, PhD •

Av. Princesa Leopoldina 19/402, CEP 40.150-080, Salvador, Bahia - Brasil

E-mail: lccorreia@terra.com.br

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Methodology

Sample selection

We evaluated the carotid arteries of 60 female volunteers, aged over 18 years and BMI ≥ 25 kg/m², from the Ambulatório de Obesidade Docente Assistencial da Escola Bahiana de Medicina and Public Health, in the year 2012. The study was approved by the Ethics Committee in Research of the Pesquisa da Escola Bahiana de Medicina and Public Health, in accordance with the Helsinki Declaration. For this research, one participant was excluded due to inadequate image for measurement of carotid intimo-medio complex resulting 59 tests for analysis.

Study Protocol

All participants answered a clinical structured questionnaire and had their anthropometric data and physical examination recorded. Laboratory tests were performed in 12-hour fasting, following standardized procedures by the Brazilian Society of Clinical Pathology/Laboratory Medicine – SBPC/ML.

Ultrasonography of the carotid arteries was performed with the patient in supine position, head rotated to the contralateral side at 45º of the midline and minimum support below the neck. The right and left arteries were evaluated by using a bi-dimensional ultrasound device of high resolution (Vivid 3, GE), connected with a linear transducer of 7.5MHz, following a previously validated protocol.

Initially, longitudinal and transverse scans of the right and left carotid arteries were acquired starting from their origin, through the bulb, fork, until the branches. Longitudinal images were obtained in the distal cm of segment of the Right Common Carotid Artery (RCCA), pre-bulbar region, focusing on the wall away from the transducer to research atheroma plaque and verification of the carotid intimo-medio thickness, defined as the distance between the lumen-intima and intima adventitia interfaces. The image screen was selected in diastole, at the peak of the R wave of the electrocardiogram. The CIMT measurements were performed by the manual and semiautomated methods (Figure 1).

The manual analysis of CIMT was made by the three point to point measures. The first point was positioned at the top edge of the dividing line between the lumen and the intima layer and the second point on the top edge of the dividing line between the media and adventitia layer, determined manually by the examiner, with approximately one millimeter between the measures. The manual CIMT (manualCIMT) was defined as the average of these three measurements.

As a reference standard, the semiautomated measures were performed by a software recognizing edges (Vivid 3 Pro IMT software analyzer). In this method, the measurement is started by a mouse click into the vessel lumen, at tje limit on the left side of the arterial segment of interest and delimited by a second mouse click on the right limit, with approximately one centimeter between them. The detection of interfaces lumen-intima and media-adventitia within the arterial segment delimited is done automatically based on the image, intensity and gradient information. On average, 100 samples are measured depending on the parameters of

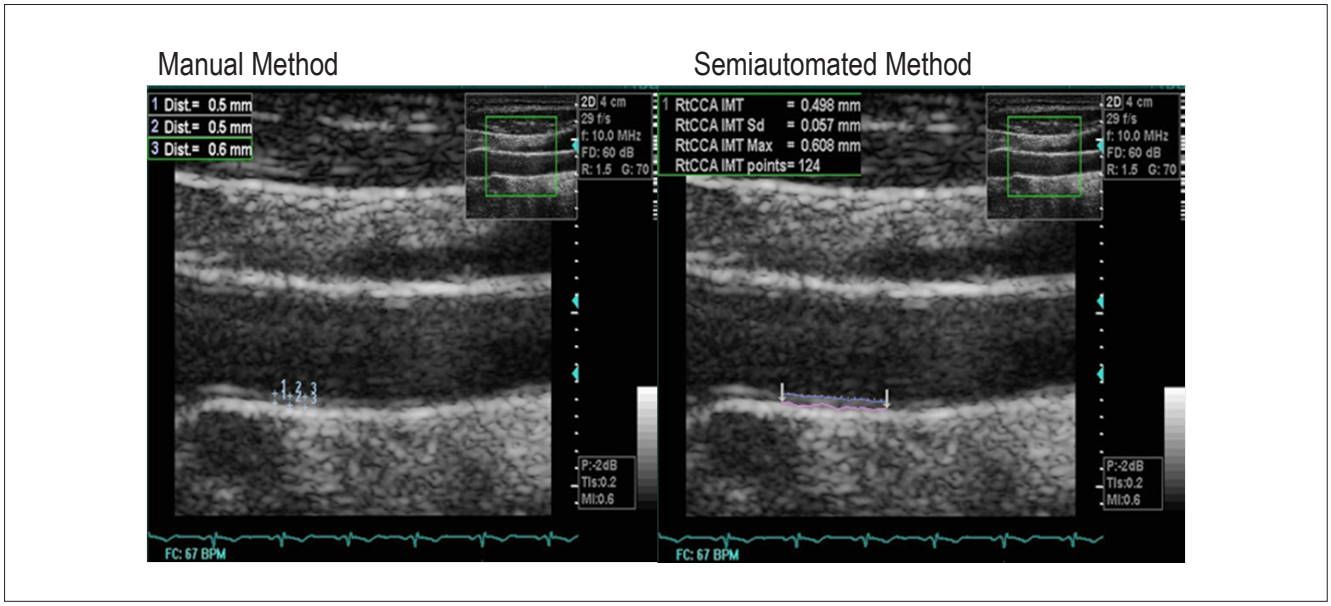


Figure 1

image acquisition, such as frequency and depth. Maximum semiautomated measures were acquired (samaxCIMT) and medium (samCIMT) of intimo-medio thickness, being samaxCIMT the measure used for analysis in this work. The high accuracy is due to the automatic use of parameters such as echo intensity and gradient intensity in repeated measures with monitoring of the linearity of the luminal contours, this being considered the reference standard method of ultrasound to measure the CIMT, with significantly lower variability.

Images collected and stored digitally by the same examiner were analyzed off-line, in a blind way, for the clinical information of the patients after completion of all the collections. A second independent examiner also completed the same measures, previously recorded. These measurements allowed data analysis.

Analysis of the data

The evaluation of the manual method was carried out by taking the maximum measurement of the semiautomated method as a reference. The linear association between manual and semiautomated methods was tested using Pearson's correlation. After this first analysis, the accuracy of the manual was assessed by the degree of agreement with semiautomated method in relation to the numeric measurement of CIMT, as well as the inter-and intraobserver variabilities in the two models were tested by applying the method of Bland and Altman in which it is graphically represented the association between the difference of the two measures (axis y) and the average between the two of them (axis x). The mean difference is calculated after removing the negative signs and limits of agreement at the level 95%, considering 1.96 standard deviations of the difference.

In addition to obtaining the agreement of the categorical methods in measuring of the subclinical atherosclerosis, we used the Kappa test. We took as a cut-off the percentil 75 percentile of the intimo-medio carotid thickness distribution in the population studied by Atherosclerotic Risk in Communities (ARIC study), which, for the age group and gender, corresponds to 0.65 mm of CIMT. It is considered from this percentil there is the presence of some degree of subclinical atherosclerosis with increased cardiovascular risk[4,11,12]. The results were considered statistically significant when $P < 0.05$ and the statistical analysis of data was performed with software Statistical Package for Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

Characteristics of the sample

We studied 59 young adult women (42 ± 9.6 years) with a BMI of 35 ± 6.4 kg/m², all with increased waist circumference (108 ± 12 cm), usually with normal blood pressure levels (134 ± 18.2 x 84 ± 12 mmHg), average glucose of 107 ± 64 mg/dL, being the average of the lipidic profile discreetly high in relation to the ideal (LDL - cholesterol 136 ± 30,1 mg/dL). The inflammatory marker PCR of high sensitivity sjpwed jogj median value (3.56 mg/L varuomg from 0.65 to 10 mg/L), consistent with the inflammatory component present. Were recorded in the population studied, 3% of smokers, 9% of type II diabetes mellitus and 46% of systemic arterial hypertension (Table 1).

CIMT values were within the normal range of average, as demonstrated by the methods manual (0.67 ± 0.11 mm) and maximum semiautomated (0.70 ± 0.12 mm). There were no atheromatous plaques in the segments evaluated.

Accuracy of the manual method

The measure of CIMT cjecled by the manual method showed a strong correlation with the semiautomated measurement ($r = 0.84$, $p < 0.0001$) (Chart 1) The average of the differences between the manual and semiautomated measurements was 0.06 ± 0,04 mm, being the limits of agreement at level 95%, between 0.09 to 0.14 mm, as

Table 1 - sample characteristics

Variable (N = 59)	Value
Age (years)	42 ± 9,6
Body mass index (kg/m²)	35 ± 6,4
Systolic Blood pressure (mmHg)	134 ± 18,2
diastolic blood pressure (mmHg)	84 ± 12
waistband (cm)	108 ± 12
Waist/hip	0,90 ± 0,06
total cholesterol (mg/dL)	213 ± 38,2
HDL-cholesterol(mg/dL)	50 ± 10,4
LDL-cholesterol(mg/dL)	136 ± 30,1
triglyceride (mg/dL)	136 ± 68
Glucose (mg/dL)	107 ± 64
PCRas (mg/L)	3,56 (5,03)*

PCRas: C protein high reaction sensitivity; (*) median and interquartile interval.

per graphic presentation by the analysis of Bland e Altman (Chart 2).In analyzing the percentage of occurrence of measures by the manual and semiautomated methods with absolute differences between them of less than 0.1 mm we detected 52 of the 59 measures, that is 88%.

A comparison of the two methods in the dichotomous definition of subclinical atherosclerosis (cutoff in the 75th percentile of the CIMT population, of 0.65 mm)[11] showed agreement of 53%, i.e., moderate (Kappa of 52%, $p < 0.0001$).

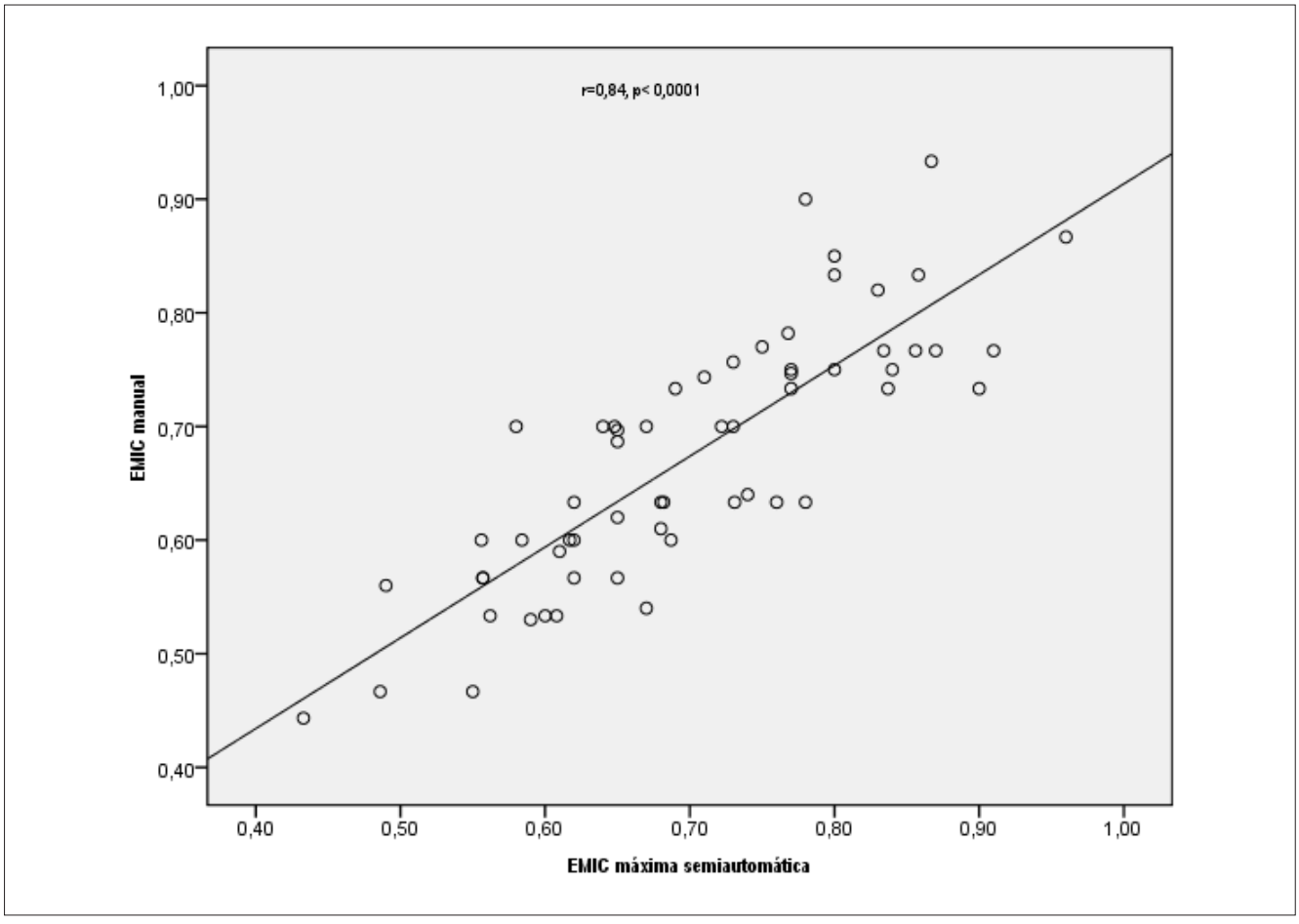
Reproducibility of manual and semiautomated methods

The correlations between the intra and interobserver measures with both methods, were at least moderate, and most showed a strong correlation (Table 2).Manual measurements of CIMT showed good intraobserver reproducibility. The mean difference was 0.04 ± 0.03 mm between two measurements made by the same observer, and the limits of agreement were at level 95% between 0.02 to 0.1 mm, while the maximum semiautomated measures showed an average of different of 0.04 ± 0,04 mm, with limits of agreement between -0,04 a 0,12 mm So intraobserver reproducibilities were similar for the manual and semiautomated methods.

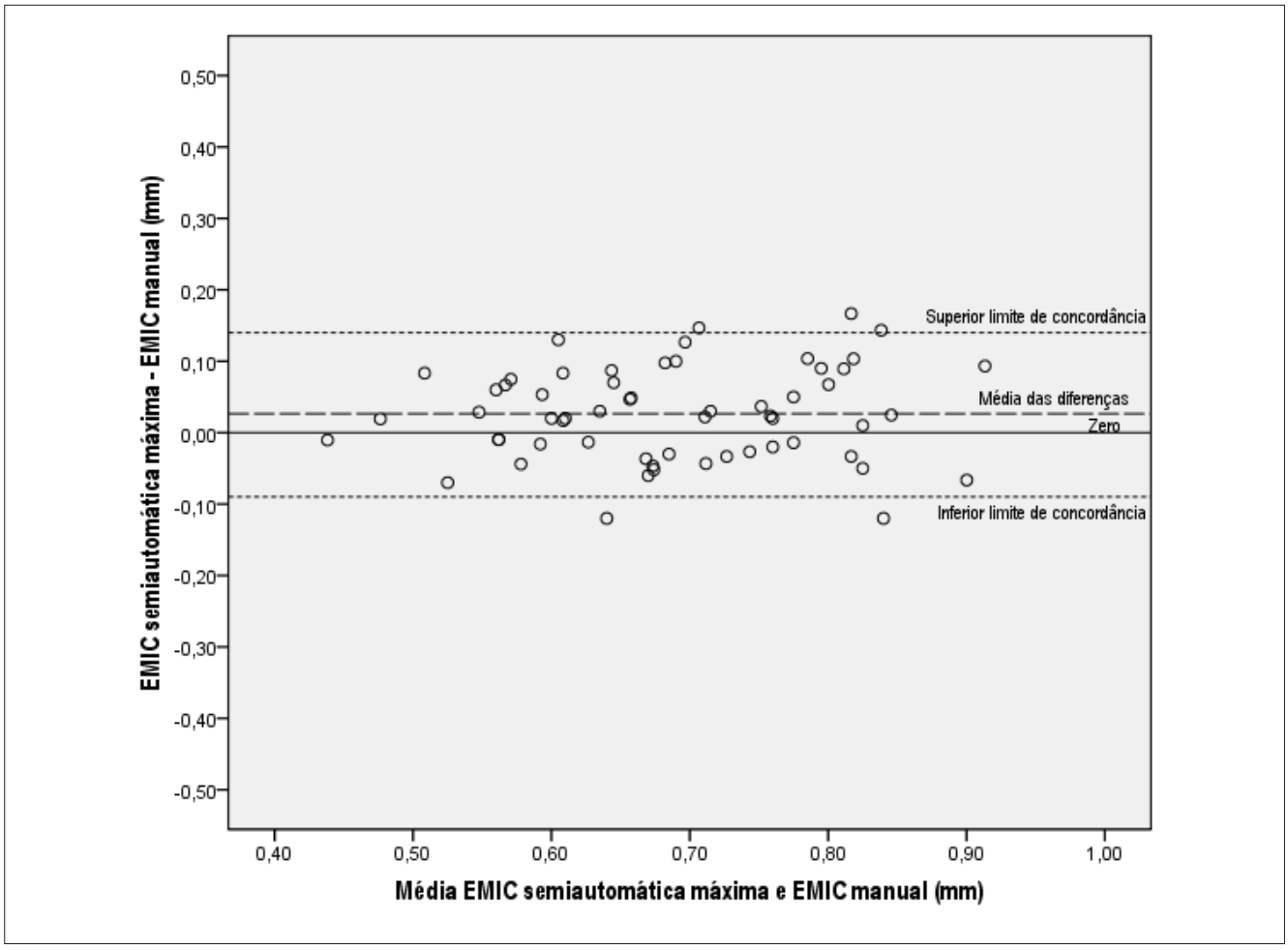
Comparison of manual measurements by two independent observers (interobserver) mean difference of 0.05 ± 0.05 mm, and the limits of agreement at the level 95% between 0.04 to 0.15 mm. The maximum semiautomated measures differed on average 0.05 ± 0.05 mm, being the limits of agreement between -0.05 to 0.14 mm. Thus, interobserver reproducibilities were similar for manual and semiautomated methods (Table 3).

Discussion

It has been demonstrated that the extent of CIMT measured by the manual method has a very good correlation with maximum semiautomated measure (r = 0.84). Data also suggest that the manual method presents moderate agreement with the maximum semiautomated, being documented a small average difference between the methods. Moreover, the limits of agreement are considered acceptable for clinical practice, and in 88% of the measures, the absolute differences between the manual and semiautomated was less than 0.1 mm. However,



Graphic 1 - *Correlation between manual EMIC with maximum semiautomatic EMI.*



Graphic 2 - *Bland-Altman's Chart comparing the values of the carotid medio-intimo thickness by the manual and semiautomated methods; Full line: zero; broken line: average of differences of 0,026 mm; dotted line: upper limits of agreement (0,14 mm) and lower (-0,09 mm).*

Table 2 - Correlation of CMIT measures – intra and interobserver

Measure	Correlation	P
Intraobserver		
manualCMIT	0,89	< 0,0001
SAmaxCMIT	0,89	< 0,0001
Interobserver		
manualCMIT	0,79	< 0,0001
SAmaxCMIT	0,86	< 0,0001

manualCMIT: carotid medio-intimo thickness by the manual method; SAmaxCMIT: maximum carotid medio-intimo thickness by the semiautomated method.

the upper limit of agreement indicates the possibility that, in some patients, significant differences occur between the two methods, especially considering the normal range of values of the thicknesses of the studied population.

The Bland-Altman analysis shows favorable results to the validation of the manual method, and the maximum semiautomated CIMT as a reference, especially taking into account the reproducibility of tje semiautomated method, i.e. taking into account the interaction between accuracy and reproducibility.

Kappa's test results confirm the findings described of mean differences, with a moderate degree of agreement with the manual method measures with the maximum measures of the semiautomated method for the cutoff of

Table 3 - Intra and interobserver reproducibility of the manual and semiautomated measures

Measure	Average of differences*	Standard deviation	Limits of agreement (95%)
Intraobserver			
manualCMIT (mm)	0,040	0,030	-0,020 - 0,100
SAmaxCMIT (mm)	0,039	0,041	-0,041 - 0,121
Interoobserver			
mamualCMIT (mm)	0,053	0,048	-0,045 - 0,149
SAmaxCMIT (mm)	0,039	0,041	-0,043 - 0,121

(*) average calculated after removal of negative signs; manualCMIT: carotid medio-intimo thickness by the manual method; SAmaxCMIT: maximum carotid medio-intimo thickness by the semiautomated method

0.65 mm[12]. Such levels of agreement can be justified when one works with predominantly low and normal values such as the measure registered herein[13].

Significant correlations were found between the measurements in the intra and interobserver analysis, which varied from 0.79 to 0.89; yet the correlation coefficient evaluates only replication relative to measures in a linear form and non-agreement between them, which is not a good indicator of reproducitiliby.

The reproducibility of measurements by both methods could be confirmed by means of the small difference averages between them, both intra-and interobserver analysis, similar to results published in the important work of reviewing 23 artigos[14] and as recommended by the Consensus of the American Society of Echocardiography in 2008, which recommends b elow 0.11 mm[8]. In addition, the limits of agreement registered were values within the range of minimum variability and agreeing with data from the Tromso Study, where the authors documented that in patients without atherosclerotic plaques, such limit is up to 0.2 mm[13].

New ultrasound techniques have evolved since the early applications of the method in the research of aterosclerosis, such as higher image resolution and also more modern technology to check the CIMT, aiming, primarily, at confering less variability of the measures, such as the case of the semiautomated technique[15]. It is important to emphasize that the Task Force of the American Society of Echocardiograph of 2008 (Consensus Statement for the American Society of Echocardiography Carotid Intima-Media Thickness Task Force) considers to be the semiautomated method the most recommended and accurate one, in addition to optimizing the time for performance of the exam[8].

The semiautomated method, however, demands financial costs related to the software used to analyze the images, and because it is more recent, it is not yet available in many image diagnostic centers. Besides this factor, in practice it is not always possible to obtain an arterial segment with image sufficiently satisfactory for obtaining semiautomated measurements, this being a limiting factor, even in the hands of experienced observers[16]. From the initial selection of 60 patients for this study, one including was excluded, exactly for this reason.

The sample consisting exclusively of young women with obesity was one of the limitations of the study and a larger study from the perspective of population will give more power to validation. One should also recognize that the comparative analysis between the methods were based on images previously acquired and stored digitally, as it is not possible to evaluate the variation related to the procedure of acquisition by the examiner. However, the primary intention of the present work was to analyze the reproducibility of the measurement of the thickness itself, not of its acquisition.

The guidance provided by the most recent Consensus[8] was to include, as part of the semiautomated CMIT measure, an ateroma plaque identified in the segment to be measured. In this condition, it is estimated that changes of the mean and maximum thickness intimo-medio semiautomated values, which prevents the comparison with simplified manual measurement. However, in the sample studied, there were not recorded plaques in the segments examined, so any inference about reliability of the measures for a scenario of higher atherosclerotic burden should not be done.

It is established that both measures of CMIT, average and maximum, provided by the semiautomated technique, are associated with cardiovascular risk factors[17,18]. In addition, in a post-hoc analysis, with the 984 subjects of the METEOR study, it was seen high reproducibility in both methods, manual and semiautomated, with similar degrees of relation with risk factors. Additionally, one registered with both

modalities a similar effect of statin therapy on the measure of CMIT[18]. Considering that the maximum measure must reflect the most advanced degree of aterosclerotic burden and that has been used in important work generating population distribution of carotid medio-intimo thickness values[19-21], it is justified here the use of this as the reference measure for comparison.

Data from this study encourage the use of semiautomated measure, standardized in large clinical trials and from which were extracted normality distribution tables of CMIT in different populations. However, the study recognizes the manual method as an alternative tool for gauging the CMIT, due to the very good correlation between both, with similar reproducibility and adequate and satisfactory agreement considering the small mean differences between the measures and the Kappa index.

Conclusion

The manual method of measuring the carotid intimo-medio thickness could be validated as an alternative method for the semiautomated sample studied. Conducting a more comprehensive study is recommended.

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