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Carotid IMT Variability (IMTV): Its Design and Validation in Symptomatic vs. Asymptomatic 142 Italian Population

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***Abstract*—The carotid intima-media thickness (IMT) is a validated marker of cerebrovascular disease risk. This work presents a new parameter, the IMT variability (IMTV), and compares the IMT and IMTV in symptomatic and asymptomatic Italian patients. 142 patients were analyzed (age 59±11.2 years, 59% males), 42 of which suffered from TIA (transient ischemic attack) or minor stroke. The lumen-intima (LI) and media-adventitia (MA) interfaces were manually traced by a Reader, and automatically traced by an automated system (AutoEdge). These interfaces were then used to measure the IMT and IMTV along the carotid wall. Wilcoxon and Pearson correlation analyses were performed. There was about a 65% correlation between the manual and automated measurements of IMT. There was no statistical difference between the manual and automated IMTV measurements (Wilcoxon signed rank, $p>0.7$). The observed mean IMT for symptomatic patients (0.83±0.44 mm for Reader vs. 0.82±0.35 mm for AutoEdge) was higher compared to asymptomatic patients (0.78±0.45 mm for Reader vs. 0.74±0.30 mm for AutoEdge). The symptomatic IMTV was about 11% higher than the asymptomatic IMTV when using Reader tracings and 8% higher when using AutoEdge. AutoEdge was very accurate in measuring the IMT and IMTV both for symptomatic and asymptomatic patients. Results showed that the symptomatic subjects had comparable IMT with respect to asymptomatic subjects, but a higher IMTV value.**

I. Introduction

The intima-media thickness (IMT) of large arteries can help monitor atherosclerotic progression [1]. Particularly, the common carotid artery IMT has proven a suitable non-invasive indicator of atherosclerosis and is now widely accepted and used as a reliable indicator of the subject's cardiovascular risk [2].

The shortcoming of manual IMT measurements taken from ultrasound images is observer or reader variability [3]. This variability is partly due to the expertise of the sonographer reporting the images, but it can also be partly ascribed to the image artifacts (*i.e.*, calcium deposits or blood rouleaux), which make the detection of the LI/MA interfaces difficult. Recently, Polak *et al.* [4] studied the differences between computer-based LI/MA tracings and manual tracings and their associations with the Framingham risk factors. They showed that their semi-automated computer system preserved the subjects' risk factor when compared to human results and helped decrease the IMT measurement variability.

In recent studies, it was shown that the IMT variation along the carotid artery wall has a stronger correlation with atherosclerosis than the IMT itself [5]. This was justified by the fact that the IMT variation is an estimation of the wall irregularity [5], which is a risk condition for plaque buildup. Therefore, besides the computation of the carotid IMT, the quantification of the IMT changes along the vessel could be an important diagnostic tool.

Here, we measure the carotid Intima-Media Thickness Variability (IMTV), which can be quantified by measuring the variations of the IMT over a given segment of the artery. The evaluation of the IMT irregularity over a carotid segment requires the segmentation of the far carotid wall, *i.e.* the tracings of the lumen-intima (LI) and media-adventitia (MA) interfaces along the carotid wall segment.

Complete automation of the carotid wall characteristics analysis (IMT and its variation along an artery segment), not only lets the clinicians save time, but also avoids the problem of inter-reader variability. The purpose of this paper was to compare the IMT and the IMTV in Italian symptomatic and asymptomatic patients, and further to analyze the role of the IMTV in understanding the nature of the atherosclerotic disease. We also try to address if IMTV could be a better predictor for cerebrovascular symptoms.

II. Materials and Methods

A. Patients Demographics

This is a prospective study and the Institutional Review board (IRB) approval was obtained. One hundred and forty two consecutive patients (84 males, 58 females; mean age 59 years; age range 35-76 years) were enrolled in this study between February 2011 and August 2011. All patients underwent ultrasound B-mode examinations for the study of carotid arteries. The inclusion criteria for the study was the presence of cerebrovascular symptoms such as TIA (transiet ischemic attack) or stroke in the patients, or patients who underwent cardiac interventions for coronary artery disease, aortic interventions, lower leg artery surgery, or were diabetic and > 50 years old.

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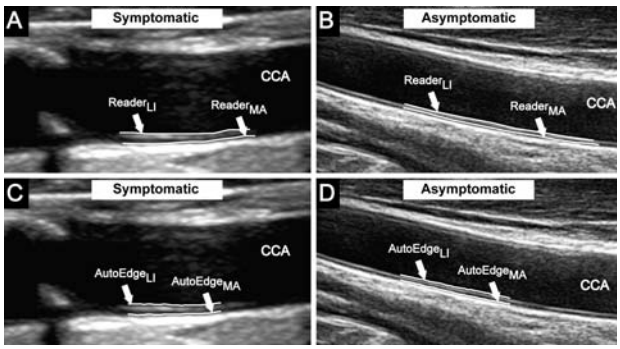

Fig. 1. Manual (first row) and automated (second row) LI/MA tracings for a symptomatic (left column) and an asymptomatic (right column) patient. $Reader_{LI}$ and $Reader_{MA}$ indicate the LI and MA manual tracings, respectively. $AutoEdge_{LI}$ and $AutoEdge_{MA}$ indicate the LI and MA tracings obtained with the AutoEdge technique, respectively.

TIA was regarded as an episode of neurological dysfunction (hemiparesis, hemiparesthesia, dysarthria, dysphasia or monocular blindness) not exceeding 24 hours. If the episode of neurological dysfunction exceeded 24 hours it was classified as a stroke. The time window to be included in the symptomatic group was 6 months; when a patient underwent a US examination more than 6 months after the TIA or stroke, they were excluded from the symptomatic group and were included in the asymptomatic group.

B. Ultrasound Technique and Analysis

Our image dataset consisted in 142 ultrasound B-Mode images of the common carotid artery (CCA). All images were taken approximately at 1 cm from the carotid bulb. One sonographer acquired all the images and optimized the scanner settings (focusing, image depth, gain, TGC settings, dynamic range) for each patient. All of the images were acquired with a MyLab70 (Esaote, Genova, Italy) scanner equipped with a linear 8-15 MHz probe, and were digitized on 8 bits (256 gray levels) and then exported in DICOM format. In the symptomatic patients the carotid concordant with the cerebrovascular symptoms was selected for the examination, whereas in the asymptomatic patients the carotid was randomly selected (right or left).

An expert sonographer (later called Reader), with more than 10 years of experience in vascular ultrasound imaging, manually traced the LI and MA borders in all 142 images by using dedicated software (ImgTracer™, Global Biomedical Technologies (GBTI), Inc., CA, USA) [6]. Figures 1.A and 1.B show the manual tracings of the LI and MA interfaces for a symptomatic (1.A) and an asymptomatic (1.B) patient.

C. Automated LI and MA Tracing

The details about the edge detection technique we used to obtain the automated IMT and IMTV measurements (AutoEdge), can be found in previous publications [7, 8]. It is a completely automated procedure for carotid distal (far) layers extraction, which is based on an integrated approach using gradient information and line fitting approach, consisting of two parts: (1) *Stage-I*: a module that automatically identifies the CCA in the image; (2) *Stage-II*: a delineation procedure that automatically traces the LI and the MA contours of the distal wall in the region of interest of the identified CCA.

In *Stage-I*, AutoEdge exploits the hypothesis that the far adventitia is the brightest feature in the B-Mode image, a hypothesis we recently validated on an image database of 200 images [9]. Output of *Stage-I* is the tracing of the far adventitia profile (AD_F), which is used as a marker of the position of the carotid artery in the image. In *Stage-II,* the far wall is segmented by using a fuzzy *K-means* classifier that automatically finds the boundary between the lumen and the intima, and then between the media and the adventitia layers. Figures 1.C and 1.D show the final AutoEdge delineations of the LI and MA interfaces for a symptomatic (1.C) and an asymptomatic (1.D) patient. This system runs a complete image analysis in about 1 s per image and is independent on the scanner settings and equipment manufacturer [8].

D. IMT Distance Metric and IMT variability (IMTV)

The carotid IMT value was measured as the distance between the LI and the MA boundaries. We used the Polyline Distance Method (PDM) as a distance metric [10].

The basic idea of the PDM is to measure the distance of each vertex of a boundary to the segments of the other boundary. Full details about polyline implementation and use for IMT measurement can be found in the works by Suri *et al.* [10] and Molinari *et al.*[11]. In our study, the IMT value was the PDM distance between the LI and MA boundary:

$$IMT = PDM\left(LI, MA\right) \tag{1}$$

We also measured the IMT variability, the IMTV, which is a measure of how variable the distance between the vertices of LI from the segments of MA is, and vice versa. So, if we define σ_{LI} as the standard deviation of the distances of the vertices of LI from the segments of MA, and σ_{MA} as the standard deviation of the distances of the vertices of MA from the segments of LI, the IMTV can be defined as:

$$IMTV = \frac{N_{LI} \cdot \sigma_{LI} + N_{MA} \cdot \sigma_{MA}}{N_{LI} + N_{MA}} \tag{2}$$

where N_{LI} and N_{MA} are the number of vertices of LI and MA, respectively.

We chose the PDM metric because it ensures a robust estimation of the actual distance between two boundaries even in presence of curved or inclined delineations. The IMTV is a measure of variability of the distance between two profiles and, in our case, of the irregularity of the distal wall interfaces.

E. Statistical Analysis and Error Computation

After verifying the normality of the distribution of the IMT and IMTV values, we used the Student's *t-test* to find the difference between the symptomatic and asymptomatic IMT and IMTV values. Using the Wilcoxon signed rank test, we assessed the difference between the IMT and IMTV values of the Reader and AutoEdge. We applied the Bonferroni

correction for multiple tests. For all the tests we considered a first-species error of 5% (*i.e.* $\alpha = 0.05$).

III. Results

As a first result, our AutoEdge system automatically processed the 142 images of the database, tracing the LI/MA profiles for all of the images.

The Reader's IMT values for symptomatic and asymptomatic patients were 0.83±0.44 mm and 0.78±0.45 mm, respectively. The AutoEdge IMT values were 0.82±0.35 mm and 0.74±0.30 mm for symptomatic and asymptomatic patients, respectively. So, the agreement between the Reader and AutoEdge IMT measurements was 98.7% for the symptomatic patients and 94.9% for the asymptomatic patients. Both the Reader and AutoEdge showed a higher IMT value for the symptomatic patients, but they did not prove to be statistically significant ($p>0.5$ for the Reader's value and $p>0.7$ for AutoEdge). The IMT values of AutoEdge were not statistically different from those manually measured ($p>0.11$ for the symptomatic patients and $p > 0.15$ for the asymptomatic group). The correlation between the Reader and AutoEdge IMT values was equal to 0.68 (C.I. 0.45 – 0.82) for the symptomatic patients and 0.65 (C.I. 0.51 – 0.76) for the asymptomatic patients. Figure 2 shows the Bland-Altman plots of the Reader and AutoEdge IMT values. It is possible to observe that there is no trend or bias of AutoEdge compared to human tracings neither in the symptomatic patients group (Fig. 2.A) nor in the asymptomatic one (Fig. 2.B).

Table 1 summarizes the IMTV values that were obtained from the Reader LI/MA tracings (first row) and from AutoEdge tracings (second row) on the symptomatic (first column) and asymptomatic (second column) groups. Both from AutoEdge and Reader LI/MA tracings, the IMTV of the symptomatic subjects was higher than that of the asymptomatic subjects. Considering the Reader LI/MA tracings, the symptomatic IMTV was about 11% higher than that of asymptomatic and for AutoEdge tracings, it was about 7.7% higher. So, there was an overall good agreement between the IMTV values of AutoEdge and those of the human operator. Figures 2.C and 2.D report the Bland-Altman plots between the Reader IMTV and the AutoEdge IMTV, showing that there was an overall good accordance between the two measurement sets, even though there was a higher variability in the IMTV measurement of the symptomatic patients.

IV. Discussion

In this paper we analyzed 142 B-Mode ultrasound images of carotid arteries. 100 were relative to asymptomatic patients and 42 to symptomatic patients. An expert Reader manually segmented the LI/MA borders in the carotid images. We compared the carotid IMT values derived from the manual LI/MA delineations with those we measured from the LI/MA interfaces detected by a completely user-independent computer-based automated system called AutoEdge.

TABLE 1 - IMT VARIABILITY (IMTV) VALUES MEASURED BY THE READER AND BY AUTOEDGE ON THE TWO SUBGROUPS OF PATIENTS: SYMPTOMATIC AND ASYMPTOMATIC. THE VALUES ARE EXPRESSED AS MEAN VALUE ± STANDARD DEVIATION.

Manual vs. AutoEdge Method	Symptomatic (42 images)	Asymptomatic (100 images)	Percent above Asymp.
Reader IMTV (mm)	0.18 ± 0.11	0.16 ± 0.06	11.1%
AutoEdge IMTV (mm)	0.13 ± 0.05	0.12 ± 0.05	7.7%

From the point of view of the performance of the computer system, AutoEdge obtained IMT and IMTV values that were very close to those measured by the Reader. The average IMT bias (*i.e.,* the average difference between the Reader's IMT measurement and the AutoEdge IMT measurement) was equal to 0.07±0.33 mm for the symptomatic patients and 0.04±0.39 mm for the asymptomatic patients. The statistical analysis revealed a correlation higher than 60% and the Bland-Altman plots (Fig. 2) documented the absence of a trend. As can also be observed, the IMT difference is zero-mean distributed and AutoEdge has a slight tendency towards overestimation of the IMT in 6 images (about 4% of the total). Therefore, according to the IMT measurements, the user-independent AutoEdge system proved to be very accurate. Therefore, using the IMT values measured by AutoEdge instead of those measured by the Reader would preserve the patients' cardiovascular risk factor linked to the IMT value.

A direct comparison of this performance in terms of IMT estimation with literature is not straightforward. However, the best-performing computer system we found in literature was based on an edge detector and was proposed by Faita *et al.* [12]. This system had very high accuracy showing an IMT error as low as 0.01 mm. However, as a drawback, this technique was user-dependent. Among the fully automated systems, AutoEdge showed performance in line with the most advanced methods (see Molinari *et al.* [13] for a review on the IMT measurement systems performance), with IMT measurement errors equal to about 0.05 mm on average.

From the point of view of the IMT variability (IMTV) measurement, AutoEdge again showed a very accurate performance. Even though the IMTV values measured by AutoEdge were different from those obtained by the Reader (0.18 mm vs. 0.13 mm ~ 27% for symptomatic and 0.16 mm vs. 0.12 mm ~ 25% for asymptomatic), the association between the IMTV and the presence of symptoms were consistent. In fact, another important result of this study was the association of the IMTV with cardiovascular symptoms. For both the Reader and AutoEdge, the distance between the traced LI/MA borders was more variable in the case of symptomatic patients, giving forth a higher IMTV value. This suggests that there could be a correlation between IMTV and the presence of cardiovascular symptoms, which was already hypothesized in previous studies [5].

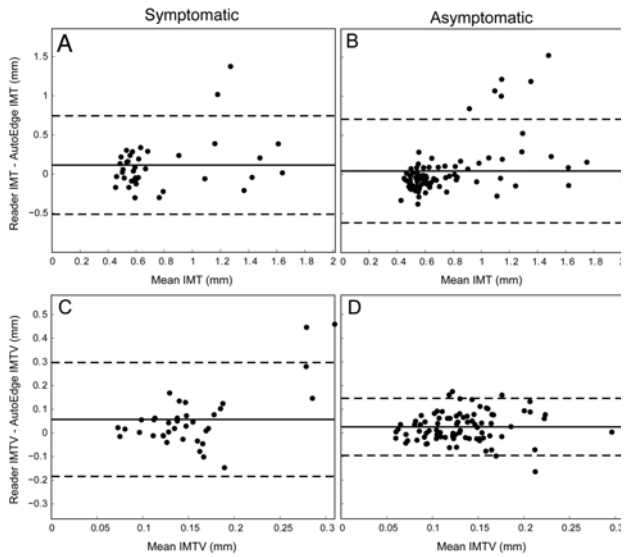

Fig. 2. Bland-Altman plots for the symptomatic (first column) and asymptomatic (second column) groups derived from the Reader IMT (panel A) and AutoEdge IMT (panel B) values and the Reader IMTV (panel C) and AutoEdge IMTV (panel D) values. The continuous lines represent the IMT difference mean value; the dashed lines represent the mean value ± one standard deviation.

Ishizu *et al.* [14] quantitatively evaluated the irregularity of the IMT and showed that the evaluation of the IMT irregularity or variability by ultrasonography is a useful predictor for the presence of coronary atherosclerosis. Their quantitative evaluation was, however, based solely on manual measurements.

Labropulos *et al.* [15] showed that the IMT and wall irregularity are associated to an increased cardiovascular risk. In their study, however, the IMT was manually measured and the wall variability was only qualitatively assessed visually. This further points out the need for a quantitative characterization of the carotid far wall irregularity in studies regarding the assessment of the subjects' risk score.

Polak *et al.* [4, 16] determined the effect of the LI/MA tracings on the assessment of the vascular age and on the measurement of the carotid IMT. They demonstrated the need and the advantage of using computer systems to aid the clinicians. This system, however, must preserve the cardiovascular risk as well as be accurate and reproducible as a measurement tool [4].

V. Conclusions

We analyzed the IMT and IMT variability (IMTV) of 142 longitudinal ultrasound carotid B-Mode images. The IMT and IMTV values were measured with manually traced LI and MA delineations and with automatically traced computer delineations (AutoEdge). We showed that AutoEdge was very accurate in measuring the IMT and in preserving the IMTV value both in presence and absence of symptoms. From a clinical point of view, we showed that the symptomatic subjects showed a comparable IMT when compared to asymptomatic subjects, but a higher IMTV value by 11% using manual delineations, and 8% using the AutoEdge system borders. We showed that AutoEdge is a powerful system, which preserves the cardiovascular risk when both IMT and IMTV are used.

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