CARES 2.0: Completely Automated Robust Edge Snapper for CIMT Measurement in 300 Ultrasound Images—A Two Stage Paradigm

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The carotid intima-media thickness (IMT) is a widely used marker associated to the risk of cardiovascular diseases and to atherosclerosis progression. IMT measurement requires high accuracy and reproducibility. Computer-aided measurements improve accuracy and precision, but usually require user interaction. In this paper we proposed an improved method (called CARES 2.0) over the previously developed technique (called CARES 1.0). CARES 2.0 is a two stage process: Stage-I adapts an integrated approach of intelligent image feature extraction and line fitting for far adventitia border detection. Stage-II is a first order absolute moment (FOAM 1.0) coupled to a novel and improved heuristic search for the lumen-intima (LI) and media-adventitia (MA) peaks. CARES 2.0 brings in two novel scientific contributions: (a) ability to improve Stage-I to compare jugular vein versus carotid artery and (b) introduce bi-directional and robust FOAM. The improved method is a fully automated IMT measurement technique, and was validated on a multi-institutional database of 300 images exhibiting normal and pathologic carotids. We benchmarked CARES 2.0 against previously developed CALEX 1.0 and user-driven FOAM 1.0 CARES 2.0 showed an IMT measurement bias equal to $-0.032 \pm 0.178$ mm, which was better than CALEX 1.0 ($0.070 \pm 0.331$ mm), FOAM 1.0 ($-0.091 \pm 0.161$ mm) and CARES 1.0 ($0.035 \pm 0.198$ mm), respectively. Thus CARES 2.0 showed an improvement of 54% over CALEX 1.0, 65% over stand alone FOAM 1.0 and 9% over CARES 1.0. Compared to CARES 1.0, CARES 2.0 improved the reproducibility by 10%. CARES 2.0 ensured complete automation and increased the reproducibility of the IMT measurement, a step closer for clinical usage.

Keywords:

1. INTRODUCTION

The intima-media thickness (IMT) of the carotid artery (CA) is widely used as a risk marker for cardiovascular diseases.4–7 Specifically, the carotid IMT is a reliable indicator of the progression of atherosclerosis.8

In clinical practice, IMT is usually measured by using ultrasound imaging. Ultrasounds are a non-ionizing radiations and the ultrasound scanner economic compared to other imaging devices (e.g., CT, MR and X-ray). Ultrasounds, however, are a user-dependent methodology. Also, the IMT is manually measured by the sonographer. Manual measurements, besides being subjective, decrease the reproducibility of the IMT evaluation, they are time consuming and prone to errors and inaccuracies. Due to these limitations, several research groups developed computer-based techniques for the IMT measurements from ultrasound images.

Most of the developed techniques are semi-automated and require some level of user interaction. To measure the IMT of the CA, the sonographer acquires a longitudinal image of the artery and then manually measures the IMT value on the distal wall by placing two markers. The first marker is placed in correspondence of the interface between the lumen and the intima (LI), the second marker in correspondence of the transition between the
The B-Mode longitudinal image of the CA contains also other tissues and, often, the jugular vein (JV). Therefore, the semi-automated measurement has the advantage that the user locates the CA far wall and the computer method traces the LI/MA profiles. User-dependent techniques showing very good performance in IMT measurement were proposed by Faita et al.,19 Stein et al.,11 Cheng et al.,12 Loizou et al.,13 Liang et al.14 and Rocha et al.15 In the above-mentioned techniques, the user must mark the position of the carotid artery in the image frame, in order to initialize the algorithm.

Many research teams faced the challenge of full automation.2,16–20 Conceptually, automated techniques consist of two stages:

• Stage-I: carotid artery recognition and localization in the B-mode image frame;
• Stage-II: far (distal) wall segmentation and LI/MA profiles tracing.

Golemati17 used the Hough transform to automatically locate the far wall of the carotid artery in the image frame. Rossi et al.18 adopted a template-matching algorithm coupled to a clustering technique, which automatically traced the centerline of the CA lumen. Delsanto et al.16 presented an automated method for lumen detection of the carotid artery by using local statistics and signal analysis. Molinari et al.2 proposed an integrated approach based on image feature extraction, fitting, and classification (which was named as CALEX 1.0, representing generation 1.0), which traced the profile of the far adventitia layer (ADF).

All the above-mentioned automated methods still suffer from some limitations:

(1) The ultrasound images are corrupted by a particular noise source called speckle noise. Even if different despeckling filters have been optimized for carotid imaging (see the comparison made by Loizou et al.21), speckle noise can still be a limiting factor for automated lumen recognition.

(2) The JV is often present in the image and located above the CA. JV can be a confounding factor both for lumen detection and far adventitia layer (ADF) tracing.

(3) Another noise source is blood backscattering. Backscattering by blood cells increases the gray level of the CA lumen, thus decreasing the performance of automated techniques based on lumen detection.

(4) Finally, the geometric shapes of the arteries pose a challenge all along the artery in automated methods, especially, if the shape changes from convex to concave to upslope to down slope shapes in the image frame.

Due to these possible limitations, it is very difficult to reach 100% accuracy in CA recognition. Above and beyond the accuracy measure, automated methods must show high reproducibility. Accuracy (i.e., the difference between the actual IMT value (traced by the physician) and the estimated one) is of paramount importance for clinical applicability. Currently, semi-automated methods reach accuracies of about 0.01 mm (about 1% of the IMT nominal value, which is 1 mm), whereas automated techniques reach accuracies of about 0.03 mm.20 (about 3% accuracy). Reproducibility (also called precision) is represented by the standard deviation (SD) of the IMT measurement errors. The lower the SD of IMT, the higher the reproducibility of the technique. Again, semi-automated techniques (which have reproducibility around 1%) outperform automated ones (which have reproducibility around 5–6%). There is, therefore, a scope of improvement to make automated techniques fully adapted for clinical scenario.

Recently we presented an IMT estimation method that was named as CARES (Completely Automated Robust Edge Snapper, called CARES 1.0).1 IMT was the distance between LI and MA borders, measured using Polyline Distance Method (PDM). This paper presents an improved version of CARES model (called as CARES 2.0) that uses the lumen region as a marker to ensure that the ADF is always on the far side of the CCA and physically below the far wall. The lumen is identified using a statistical classification procedure. Thus our major contributions in this paper are: (a) Improved and robust CARES system design; (b) Superior cascaded Stage-I and Stage-II sub-systems by introducing a check for a false far adventitia borders in Stage-I and a bi-directional FOAM in Stage-II; (c) Higher accuracy of CARES 2.0 compared to FOAM 1.0, CALEX 1.0 and CARES 1.0; (d) Superior reproducibility (precision); (e) Benchmarking of CARES 2.0 with CARES 1.0, stand alone CALEX 1.0 and FOAM 1.0 systems.

In this paper, CARES 2.0 is benchmarked against CARES 1.0 and two other IMT measurement techniques: the first one is a completely automated method the Authors had previously developed,2 (CALEX 1.0), and the second one is a user-driven method based on the first order absolute moment (FOAM 1.0) operator as proposed by Faita et al.3 We demonstrate that CARES 2.0 shows an IMT measurement bias equal to $-$0.032 $\pm$ 0.178 mm, which was better than CALEX 1.0 (0.070 $\pm$ 0.331 mm), FOAM 1.0 ($-$0.091 $\pm$ 0.161 mm) and CARES 1.0 (0.035 $\pm$ 0.198 mm), respectively. Thus we will show that CARES 2.0 shows an improvement of 54% over CALEX 1.0, 65% over stand alone FOAM 1.0 and 9% over CARES 1.0. Compared to CARES 1.0, we show that CARES 2.0 has an improved reproducibility by 10%. Finally, we will show that CARES 2.0 ensured complete automation and increased the reproducibility of the IMT measurement, a step closer for clinical usage.

The paper is organized as follows: Section 2 presents the architecture for CARES 2.0 and Section 3 details the image database and the performance assessment metric. Results are reported by Section 4 and discussion in Section 5. Finally, Section 6 concludes and summarizes the improvements introduced by CARES 2.0 in terms of accuracy and reproducibility.

2. CARES 2.0 ARCHITECTURE

In this section we describe the CARES 2.0 architecture that is conceptually made of two cascaded steps: Stage-I devoted to the carotid artery recognition and Stage-II aiming at far (distal) wall segmentation and IMT measurement.

The foundation of Stage-I was a technique called CALEX 1.0 and recently proposed by Molinari et al.2,18 Stage-II was based on a robust and high-performance edge operator.22,23 which was recently adapted to the carotid artery IMT measurement by Faita et al.2 The innovative aspects of our CARES 2.0 technique are: (a) introducing a check for far adventitia borders to avoid its false far adventitia border detection and (b) the development of an original and high-performance heuristic search, which is applied to the edge detection map to trace the precise position of the LI/MA interfaces.
2.1. Stage-I: Carotid Artery Recognition (AD$_F$ Tracing)

Stage-I consists in the automated localization of the carotid artery in the image frame. We used a technique called CALEX 1.0, which we had previously developed and published. CALEX 1.0 is based on an integrated approach consisting in (a) feature extraction, (b) fitting, and (c) validation. We modeled the carotid artery as a dark region (the lumen) surrounded by two high-intensity stripes (the adventitia layers). Stage-I, thus, consists of the following sub-steps:

(a) **Feature extraction**: every local intensity maximum is processed by a linear discriminator, which analyzes intensity and breadth of each maximum. The maxima of the image that are above a given threshold are marked as *seed points*. Seed points are then connected among them to form *line segments*.

(b) **Fitting**: line segments are combined in order to form profiles. Such profiles trace the boundaries of the high-intensity features of the image with a linear aspect. An example of detected line segments from Figure 1(A) is reported in Figure 1(B).

(c) **Line segments validation**: line segments are considered in pairs to detect the two that comprise the artery lumen. Such line segments are traced in correspondence of the near and far adventitia layer. Figure 1(C) shows CALEX 1.0 automated far adventitia tracing (AD$_F$). For details on CALEX 1.0, readers are recommended to visit Molinari et al.

Pilot studies demonstrated that the traced AD$_F$ profile could be characterized by spikes and false points identification. This could be due to several reasons such as (a) presence of jugular vein due to orientation scanning; (b) variations in intensities due to variety of reasons such as probe interface with skin, frequency of operation and gain settings; (c) gaps in the media walls due to non-uniformity of the media layer; (d) shadow effects due to presence of calcium in the near wall, or combination of these. We have therefore introduced a validation and refinement protocol that provides a check on the AD$_F$ profile ensuring that the location of far adventitia segmentation edge is correct and smooth. This architecture of the validation step refines the AD$_F$ profile and is done in two steps: (a) refinement using anatomic lumen and (b) spike removal. Thus the stage-I of CALEX 1.0 has now been refined by adding these to refinement stages discussed below.

2.1.1. Lumen Region Detection via Pixel Classification

The concept is to avoid the AD$_F$ profile protruding into the lumen vessel or beyond. This requires the introduction of a check condition for AD$_F$ profile. This objective of this condition is to ensure that the AD$_F$ profile (output of stage-I) does not penetrate into the lumen region.

We have thus modeled the lumen segmentation region as a classification process of the lumen region into two classes, given a mixture model of pixel intensities. The pixels belonging to the carotid lumen can be automatically detected if the local intensities of each pixel are analyzed. This is because the (a) pixels belonging to the vessel lumen are characterized by low mean intensity and low standard deviation; (b) pixels belonging to the adventitia layer of the carotid wall are characterized by high mean intensity and low standard deviation; and (c) all remaining pixels should have high mean intensity and high standard deviation. We grouped the normalized average and standard deviation values of each pixel’s $10 \times 10$ neighborhood into 50 classes having an interval of $W_{\text{Class}} = 0.02$. In previous studies, we showed that pixels belonging to the lumen of the artery are usually classified into the first classes of this 2DH in the first 4 classes for the average value and in the first 7 classes for the standard deviation. We therefore considered a pixel as possibly belonging to the carotid lumen if its neighborhood intensity is lower than 0.08 and if its neighborhood standard deviation is lower than 0.14. Figure 2(B) shows the detected lumen region of the image in Figure 2(A). We used the lumen check to avoid incorrect tracings by CALEX 1.0. Figure 3(A) shows an example where the near wall is detected instead of the far wall. Figure 3(B) shows that by inserting lumen check, CALEX 1.0 correctly identifies the far wall.
2.1.2. Spike Detection and Removal

Small spikes can be present in the final ADF profiles. We adopted a final step of spike detection and removal in order to optimize the profiles. A spike was defined as a jump higher than 10 pixels in the ADF profiles. All the spikes were detected and substituted by the average value of the $T_{\text{spike}} = 10$ points neighboring the spiky point (5 points to the left and 5 to the right). The conversion factor of our images was 0.06 mm/pixel. Therefore, being the nominal value of the IMT about 1 mm, it means that the distance between the LI and the MA profiles is of about 16 pixels. Therefore we called a spike, a glitch in the ADF profiles, which had a value higher than about 50% the number of pixels of the IMT.

2.2. Stage-II: Domain-Based LI/MA Segmentation Strategy

Stage-II is devoted to the automated LI/MA boundaries tracing. We focus the LI/MA tracing in a region of interest (ROI) or guidance zone (GZ). Narrowing the ROI enables a more accurate LI/MA tracing and increases robustness to noise.

Overall, Stage-II consists of three cascaded steps. Step 1 consists in the creation of a ROI (or GZ) starting from the $A_{\text{DF}}$ profile, which is the output of Stage-I. In Step 2, we used a robust edge snapper to improve the representation of the LI/MA interfaces. In Step 3 we applied an original heuristic search to precisely localize the LI/MA interfaces. Finally, Step 4 consisted in a series of innovative checks on the LI/MA points in order to improve the robustness of the Stage-II (so called bi-directional FOAM). The four steps are detailed in the following.

2.2.1. Step 1: Creation of the Guidance Zone (GZ)

We built a region-of-interest (ROI) or guidance zone (GZ) around the automatically traced far adventitia $A_{\text{DF}}$ profile. Our GZ had a horizontal length equal to the length of the $A_{\text{DF}}$ traced profile along the carotid artery. The GZ width must comprise the entire far wall (i.e. the media and intima layers) and a small portion of the artery lumen. Since we observed that the average diameter of the human common carotid artery was 6 mm, we decided to keep the envelope’s height $H_{\text{GZ}}$ to be around 1/3rd the lumen diameter that is about 30 pixels. Figure 4(B) shows the GZ extracted by the original image and the $A_{\text{DF}}$ profile of Figure 4(A). Table 1 summarizes all the parameters used in this paper.

2.2.2. Step 2: Edge Enhancement via Gradient of Gaussian (GoG):

We used the First Order Absolute Moment (FOAM) operator for improving the LI/MA edges representation in the automatically designed guidance zone. The FOAM operator is a regularized edge-based operator, which was first introduced by Demi et al. and then extended by Faita et al. to the semi-automated IMT measurement in ultrasound images. In the following, we briefly summarize the FOAM concept.

Considering an ultrasound image $I(x, y)$ and two circular domains having radiuses equal to $\theta_1$ and $\theta_2$, respectively, the FOAM edge $e(x, y)$ operator is mathematically defined as:

$$e(x, y) = \int_{\theta_2}^{\theta_1} \int [I_1(x, y) - I(x-k, y-l)] \cdot G(k, l, \sigma) dk dl$$

where $I_1(x, y) = \int_{\theta_1}^{\theta_2} I(x-k, y-l) \cdot G(x, y, \sigma) dk dl$ and is computed by low-pass filtering the input image by a Gaussian kernel with standard deviations equal to $\sigma_1$ and domain region equal to $\theta_1$. The FOAM operator represents the spatial distribution of the variability of the intensity levels of the points in the
domain $\theta_i$ with respect to the average of the domain $\theta_i$,\textsuperscript{23} which is regularized by a Gaussian kernel with standard deviation equal to $\sigma_i$.

The FOAM operator $e(x, y)$ corresponds to an edge-map. In homogeneous regions (i.e., in regions without intensity changes and that are of the same gray level), the FOAM edge value is close to zero, whereas when computed in proximity of an intensity gradient, the FOAM edge value rises to a maximum.

Gemignani et al.\textsuperscript{23} optimized the values of $\theta_1$ and $\theta_2$ for ultrasound vascular images and suggested to link the Gaussian Kernel sizes to the image resolution.\textsuperscript{23} Also, they suggested using all the $\sigma$ values equal to $1/3$rd of the kernel size.

Faita et al. showed that better robustness to noise can be achieved by adopting a third Gaussian Kernel function and proposed adopting the following modified definition of FOAM:\textsuperscript{3}

$$e(x, y) = \int_{\theta_1}^{\theta_2} \left| I_1(x, y) - I_2(x - k, y - l) \right| \cdot G(k, l, \sigma) \, dk \, dl$$

where $I_1(x, y) = \int_{\theta_1}^{\theta_2} I(x - k, y - l) \cdot G(k, l, \sigma_1) \, dk \, dl$ and $I_2(x, y) = \int_{\theta_1}^{\theta_2} I(x - k, y - l) \cdot G(x, y, \sigma_2) \, dk \, dl$ are computed by low-pass filtering the input image by a Gaussian kernel with standard deviations equal to $\sigma_1$ and $\sigma_2$, respectively. The use of two different aperture values $\sigma_1$ and $\sigma_2$ implements a filter that is similar to the Gradient-of-Gaussians (GoG) filter, which is a high-pass filter, enhancing the intensity edges.

We linked the Gaussian Kernel sizes and $\sigma$ values to the image conversion factor $\tau$ (the best conversion factor was 0.06 mm/pixel, as reported by Table II), and chose the value of $\Gamma = 0.3$ mm as pixel conversion factor for the FOAM operator. Hence, we used the kernel size $\theta_1 = \Gamma / \tau = 0.3/0.06 = 5$ pixels. As suggested by Faita et al.,\textsuperscript{3} we took $\theta_2 = 2\theta_1 = 10$ pixels. The Gaussian Kernel parameters were then taken equal to $\sigma_1 = \theta_1/3 = 2$ pixels and $\sigma_2 = \theta_2/3 = 3$ pixels. The value of 0.3 mm value was similar to that adopted by Faita et al., who used a value of 0.28 mm (see Ref. [3]). We observed that higher values originated larger Gaussian Kernels, which decreased the accuracy of the LI/MA representation and, therefore, decreased the FOAM localization performance. Conversely, values lower than 0.3 mm originated very small Gaussian Kernels, which did not ensure sufficient noise robustness.

Figure 4(C) shows the FOAM edge map associated to the GZ of Figure 4(B).

### 2.2.3. Step 3: Heuristic Approach for LI/MA Peak Detection

The FOAM 1.0 edge operator provides an enhanced representation of the LI/MA edge interfaces. However, it must be coupled to a robust peak detection technique in order to accurately estimate the position of the LI/MA points.

Faita et al.\textsuperscript{3} developed a heuristic search technique, which consisted of the following steps:

(a) The FOAM intensity profile of each $i$th column of the ROI was scanned in order to mark all the intensity maxima.
(b) If $\eta_{\text{MAX}}$ was the absolute maximum of the intensity profile considered, the first maximum starting from lumen that had an intensity higher than $\eta_{\text{MAX}}$. $\eta_4$ was considered as LI peak. Faita et al. tuned this numeric coefficient $\eta_4$ for a single-institution and single-scanner image database.
(c) The intensity peak which was the closest to LI and which had intensity higher than $\eta_{\text{MAX}} - \eta_4$ was considered as MA peak. Faita et al. tuned $\eta_4$ for the same image set.
Following, we will call this technique as FOAM 1.0, as this was tuned threshold, which Faita et al. took equal to 3 pixels). In the detection.

The regularization of the profiles was obtained through a series of checks, which were aimed at avoiding false LI/MA candidate points. In fact, usually the intensity of the MA interface is higher than that of the LI. Anatomically, adventitial layer is composed of fibro-cells that are linked to a matrix made of fibrous tissue and collagen. In big arteries, such as the carotids, this elastic layer is particularly developed. Therefore, the MA interface has a brighter representation with respect to LI. We called the candidate LI and MA points as: \( FOAM_\text{LI} \) and \( FOAM_\text{MA} \) (relative to the \( i \)th column). If we find that \( FOAM_\text{LI}_i > FOAM_\text{MA}_i \), then we assumed that the MA candidate point was a false candidate. As a result, we widened the guidance zone of \( \varepsilon_{BD} = 8 \) pixels towards the bottom of the image and repeated the heuristic search starting from step (c) discussed in the above Innovative Heuristic Approach. If the MA detection resulted again in a point with intensity lower than the LI candidate, then the column was discarded. Note that \( \varepsilon_{BD} = 8 \) pixels is about 0.5 mm, which is half the nominal size of the IMT. Therefore, we widened the GZ to double its search width thereby spanning below \( AD_p \), resulting in a total height equal to about 50% the IMT value. Figure 5(B) demonstrates that the LI/MA boundaries were correctly traced.

Table II. Image database and patient demographics. Characteristics of the image dataset coming for two different Institutions and relative patient demographics. The first column reports the institution, the second the number of image, the third the conversion factor, the fourth the scanner used. Finally, the last two columns report the number of patients and their demographics.

<table>
<thead>
<tr>
<th>Institution</th>
<th>Total images (N)</th>
<th>Conversion factor (( \tau ) mm/pixel)</th>
<th>Ultrasound scanner</th>
<th>Patients</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torino (Italy)</td>
<td>200</td>
<td>( \tau_{\text{Torino}} = 0.0625 )</td>
<td>ATL HDI5000</td>
<td>150</td>
<td>69 ± 16 years (50–83 years)</td>
</tr>
<tr>
<td>Nicosia (Cyprus)</td>
<td>100</td>
<td>( \tau_{\text{Nicosia}} = 0.0600 )</td>
<td>ATL HDI3000</td>
<td>100</td>
<td>54 ± 24 years (25–55 years)</td>
</tr>
</tbody>
</table>

(d) If both LI and MA peaks were found, the column was marked as “good” otherwise it was discarded. The process was then repeated for all the columns of the image.

A final stage of outlier removal was used to regularize the LI/MA profiles. Basically, this procedure performed a linear least square regression and removed all the points that had a distance higher than \( \delta_i \) from the regression line (\( \delta_i \) was another specifically tuned threshold, which Faita et al. took equal to 3 pixels). In the following, we will call this technique as FOAM 1.0, as this was the original segmentation technique proposed by Faita et al. 3

FOAM 1.0 was developed in a semi-automated framework, where the user manually traced the GZ in the far carotid wall. Also, the heuristic search and the outlier removal procedure were specifically developed under the hypothesis of a straight and horizontally placed carotid.

When FOAM 1.0 was applied to our automated framework of CARES 2.0, this heuristic search did not show acceptable results. False peaks were determined for LI/MA border points. The FOAM 1.0 was unidirectional, which was not suited to our scenario. The parameters were not optimized for databases, which have both normal and pathologic carotids. As a result, we developed an innovative and original heuristic search that offered an accurate LI/MA detection performance and we called it as FOAM 2.0.

2.2.4. Innovative Heuristic Approach for LI/MA Peak Detection: FOAM 2.0

Once the lumen had been detected, we processed each intensity column of the FOAM map \( \epsilon(x, y) \) relative to the guidance zone. The heuristic search was structured as follows:

(a) We identified all the intensity maxima of the intensity profile, which were comprised into the first 75th percentile of the intensity distribution of the FOAM column under analysis.

(b) The intensity profile was scanned from the lumen to the adventitia (downward direction). The first intensity maximum that had intensity in the 75th percentile and not in the lumen region was marked as LI candidate point.

(c) We kept all the intensity maxima that were comprised into the first 90th percentile of the intensity distribution of the FOAM column, considered between the LI point (identified in the previous step (b)) and the adventitia point (i.e., the point corresponding to the \( AD_p \) profile). The maximum closest to LI point was marked as MA candidate point.

(d) We repeated the process for all the columns of the image and the sequence of the LI and MA candidate points was then composed of the LI/MA boundaries.

2.2.5. Step 4: LI/MA Regularization and Error Checks: FOAM 2.0

The regularization of the profiles was obtained through a series of checks, which were aimed at avoiding false LI/MA candidate detection.

2.2.5.1. Bi-Directional MA detection. Figure 5(A) shows a condition possibly leading to an error in the MA detection. The \( AD_p \) was traced in-between the LI/MA profiles. In this condition, the LI point is located above the \( AD_p \), whereas the MA point is located below the \( AD_p \). Clearly, the MA point falls outside the guidance zone region and cannot be correctly identified.

We corrected this problem by looking to the intensities of the LI/MA candidates. In fact, usually the intensity of the MA interface is higher than that of the LI. Anatomically, adventitial layer is composed of fibro-cells that are linked to a matrix made of fibrous tissue and collagen. In big arteries, such as the carotids, this elastic layer is particularly developed. Therefore, the MA interface has a brighter representation with respect to LI. We called the candidate LI and MA points as: \( FOAM_\text{LI}_i \) and \( FOAM_\text{MA}_i \) (relative to the \( i \)th column). If we find that \( FOAM_\text{LI}_i > FOAM_\text{MA}_i \), then we assumed that the MA candidate point was a false candidate. As a result, we widened the guidance zone of \( \varepsilon_{BD} = 8 \) pixels towards the bottom of the image and repeated the heuristic search starting from step (c) discussed in the above Innovative Heuristic Approach. If the MA detection resulted again in a point with intensity lower than the LI candidate, then the column was discarded. Note that \( \varepsilon_{BD} = 8 \) pixels is about 0.5 mm, which is half the nominal size of the IMT. Therefore, we widened the GZ to double its search width thereby spanning below \( AD_p \), resulting in a total height equal to about 50% the IMT value. Figure 5(B) demonstrates that the LI/MA boundaries were correctly traced.

Fig. 5. Sample of the bi-directional (FOAM 2.0) LI/MA search heuristics: (A) The \( AD_p \) profile is inaccurate and traced in-between the LI/MA borders using updated version of CALEX 1.0. (B) LI/MA profiles traced by the bi-directional FOAM 2.0 heuristic search.
2.2.5.2. Adaptive LI Detection. In some images where the adventitia layer is particularly bright and saturated to white, there could be a high difference in the FOAM intensity of LI and MA. In such condition, the LI point would not be comprised in the first 75th percentile of the intensity distribution. Therefore, we ran an adaptive LI detection strategy, which modified the percentile value.

We first run our heuristic search by using the 75th percentile as intensity criterion for assigning the LI candidate. Let $N$ be the total number of columns of the guidance zone for a specific image. Let $N_{LI}$ be the number of LI candidate points at the end of the heuristic search. If we found $N_{LI} < 0.1 N$ (i.e., if the number of points of the LI profile was lower than 10% of the image columns), then we decreased the percentile intensity criterion and ran the heuristic once again. The procedure was iterated until $N_{LI} > 0.1 N$. At each iteration, the intensity criterion was relaxed by a 5% of the intensity distribution (i.e., the original intensity criterion was 75th percentile; in the second iteration the criterion was 70th percentile, in the third it was 65th percentile, and so on).

2.2.5.3. Lumen Region Detection via Pixel Classification. As discussed in the above Section 2.1.1, we introduced a lumen detection step to prevent the computer generated far adventitia profiles crossing the lumen region. We inserted the same lumen detection region to avoid the LI profile to protrude into the carotid lumen. This possible error was observed in presence of high blood backscattering in the lumen, causing a glitch of the LI/MA border to penetrate into lumen region. But using the FOAM 2.0 model, this glitch could be avoided.

2.2.5.4. Spike detection and removal. This step was merely adapted in the same paradigm just like it was adapted for the far adventitia ADs tracings, discussed in Section 2.1.2. Figure 6 shows samples of CARES 2.0 tracings using the combination of refined CALEX 1.0 and FOAM 2.0.

3. IMAGE DATABASE AND PERFORMANCE METRICS

In this section we summarize the characteristics of the image database and the performance metric we used.

3.1. Image Dataset

Our database consisted of 300 B-mode images collected from two different Institutions between December 2001 and July 2006. Two neurologists acquired the images. Both had 20 years of experience in neurosonology. Overall, images were relative to 250 patients, of which 107 were females. One hundred subjects were healthy controls. One-hundred and fifty patients were referred to the Neurology Divisions for neurological symptoms possibly related to atherosclerosis: 65 had previously diagnosed increased IMT, 50 had a carotid plaque, 20 suffered from transient ischemic attack, and 15 had minor stroke. All the images were acquired in digital format and discretized on 8 bits (256 gray levels). The complete description of the image database and of the patient’s demographics is reported by Table II. The conversion factors (i.e., the physical pixel dimension which we indicate by $\tau$ in Table II) were dependent on the ultrasound scanner used and on the scanner settings. The Institutions took care of obtaining written informed consent from the patients prior to acquiring data and the approval by the respective IRBs.

For each of the 300 images we had three manual segmentations made by expert sonographers all with at least 20 years of expertise in vascular sonography. To compute the IMT measurement bias, we obtained the average LI/MA tracings for every image (considered as ground truth—GT).

3.2. IMT Performance Metric

The IMT value for each image was computed as polyline distance between the LI and MA boundary. A detailed discussion
about the polyline distance metric (PDM) can be found in the work by Suri et al.\textsuperscript{26} By summarizing, let’s consider two boundaries \( B_1 \) and \( B_2 \). We can measure the lower distance between each vertex of the boundary \( B_1 \) and the line segments of the boundary \( B_2 \). Then, we can compute the lower distance between each vertex of the boundary \( B_1 \) and the line segments of the boundary \( B_2 \). The PDM is defined as the sum of all the distances divided by the total number of vertices of the two boundaries.

We compared the IMT values by benchmarking CARES 2.0 with two other segmentation strategies. The first one was the CALEX 1.0 automated technique.\textsuperscript{15,18} Note that CALEX 1.0 stand alone consists of two stages: ADF boundary estimation as Stage-I and fuzzy \( \text{k} \)-means classification to perform LI/MA segmentation (Stage-II). CARES 2.0 consisted of two stages, where stage-I refined version of CALEX 1.0 while stage II was FOAM 2.0. Full details and characterization of CALEX 1.0 stand alone can be found in our previous papers.\textsuperscript{2,18} The second technique that was used as a benchmark was the semi-automated strategy by Faita et al.,\textsuperscript{3} called FOAM 1.0 and was standalone. Therefore, this second technique simply consisted of FOAM, generation 1.0. We called this technique simply as FOAM 1.0 in the following, to indicate the standalone implementation of the FOAM operator as proposed by Faita et al.\textsuperscript{3} We computed the IMT value of each image using each of these three methods (FOAM 1.0, CALEX 1.0 and CARES 2.0). The IMT estimates were then compared to the ground truth IMT values traced by manually. We also computed the overall average distance between the LI/MA profiles of the three techniques and the corresponding ground-truth profiles (GT-LI/GT-MA).

4. RESULTS

We benchmarked CARES 2.0 with CALEX 1.0, FOAM 1.0, and CARES 1.0\textsuperscript{1} on the 300 image database. Stage-I was successful on 295 out of 300 images (98.3% success). According to previous studies,\textsuperscript{15,19,27} we defined the CA as correctly recognized in the image frame if the distance between the automated tracing of the AD\textsubscript{0} and the manually traced MA boundary was lower than 2 mm (which is a value about twice that of the average IMT). Being manually driven, FOAM 1.0 segmented all the images of the dataset. Therefore, in the following, the average IMT values for CALEX 1.0 and CARES 2.0 was on 295 images, whereas for FOAM 1.0, was on 300 images.

4.1. A Distal Wall Segmentation and Performance Evaluation

Table III reports the comparative performance evaluation using four different techniques. The second column reports the number of images correctly processed, the third column shows the PDM between LI and GT-LI, whereas the fourth column shows the PDM between MA and GT-MA. FOAM 1.0 showed LI and MA distances equal to 0.235 ± 0.406 mm and 0.255 ± 0.423 mm, respectively. CALEX 1.0 showed values equal to 0.325 ± 0.329 mm for the LI interface and 0.343 ± 0.333 mm for the MA. CARES 1.0 showed LI/MA segmentation errors equal to 0.245 ± 0.239 mm for LI and 0.256 ± 0.246 mm for MA. CARES 2.0 showed distances of 0.259 ± 0.286 mm for the LI interface and 0.250 ± 0.267 mm for the MA. The best performing techniques was FOAM 1.0 for the LI interface and CARES 2.0 for the MA. However, the average values were not statistically different among the three techniques (Student’s t-test, \( p > 0.35 \)).

Figure 7 shows comparative segmentation samples of the following three techniques: the top row is for FOAM 1.0, the middle row is for CALEX 1.0, and the bottom row is for CARES 2.0.

4.2. IMT Measurement Error

The fifth column of Table III reports the IMT measurement bias (i.e., the average difference of the IMT estimates with respect to the GT IMT values). FOAM 1.0 showed a IMT bias of \(-0.091 ± 0.161\) mm, CALEX 1.0 of \(0.070 ± 0.331\) mm, CARES 1.0 of \(0.035 ± 0.198\) mm, and CARES 2.0 of \(-0.032 ± 0.178\) mm. CARES 2.0, therefore, showed the lowest bias in IMT measurement. FOAM 1.0 showed a SD of 0.161 mm, which was slightly lower than that of CARES 2.0 (0.178 mm). The main reason being the user-controlled segmentation. CARES 2.0 showed a greater reproducibility with respect to CALEX 1.0 and CARES 1.0, the completely automated techniques.

Figure 8 shows the Bland-Altman plots for the three techniques of FOAM 1.0 (Fig. 8(A)), CALEX 1.0 (Fig. 8(B)), CARES 1.0 (Fig. 8(C)), and CARES 2.0 (Fig. 8(D)). It is possible to observe that CARES 2.0 is the technique showing the lower bias. Moreover, CARES 2.0 has a SD that is very similar to that of manual FOAM 1.0.

Figure 9 reports the histogram distribution of the IMT measurement error for the three techniques of FOAM 1.0 (Fig. 9(A)), CALEX 1.0 (Fig. 9(B)), CARES 1.0 (Fig. 9(C)), and CARES 2.0 (Fig. 9(D)). The black line above the bars represents the cumulative function of the IMT measurement error. It is possible to observe that CARES 2.0 shows the best performance, given by a very concentrated IMT error and a very steep cumulative function.

Table IV summarizes the average IMT values computed on the image dataset. The third column reports the IMT estimates by the four techniques and the fourth column reports the corresponding IMT value as obtained by the Ground-Truth profiles. Another

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**Table III. Distal wall segmentation performance. Average distances between the LI/MA profiles and the Ground-Truth LI/MA profiles for the three (FOAM, CALEX 1.0 and CARES) techniques. The fifth column reports the IMT error and the sixth the percentage improvement (mean value/standard deviation) of CARES 2.0 w.r.t. FOAM 1.0, CALEX 1.0, and CARES 1.0.**

<table>
<thead>
<tr>
<th>Techniques</th>
<th>N</th>
<th>LI error (mm)</th>
<th>MA error (mm)</th>
<th>IMT (mm)</th>
<th>Percentage improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOAM 1.0</td>
<td>300</td>
<td>0.235 ± 0.406</td>
<td>0.255 ± 0.423</td>
<td>−0.091 ± 0.161</td>
<td>64.8%/−9.6%</td>
</tr>
<tr>
<td>CALEX 1.0</td>
<td>295</td>
<td>0.325 ± 0.329</td>
<td>0.343 ± 0.333</td>
<td>0.070 ± 0.331</td>
<td>54.3%/46.2%</td>
</tr>
<tr>
<td>CARES 1.0</td>
<td>294</td>
<td>0.245 ± 0.239</td>
<td>0.256 ± 0.246</td>
<td>0.035 ± 0.198</td>
<td>8.6%/10.1%</td>
</tr>
<tr>
<td>CARES 2.0</td>
<td>295</td>
<td>0.259 ± 0.286</td>
<td>0.250 ± 0.267</td>
<td>−0.032 ± 0.178</td>
<td>—</td>
</tr>
</tbody>
</table>
method for assessing the overall IMT measurement accuracy is the Figure-of-Merit (FoM). The FoM can be expressed as:

\[
\begin{align*}
    F_{oM}^{FOAM} & = 100 - \frac{|GT_{IMT} - FOAM_{1IMT}|}{GT_{IMT}} \cdot 100 \\
    F_{oM}^{CALEX1} & = 100 - \frac{|GT_{IMT} - CALEX_{1IMT}|}{GT_{IMT}} \cdot 100 \\
    F_{oM}^{CARES1} & = 100 - \frac{|GT_{IMT} - CARES_{1IMT}|}{GT_{IMT}} \cdot 100 \\
    F_{oM}^{CARES2} & = 100 - \frac{|GT_{IMT} - CARES_{2IMT}|}{GT_{IMT}} \cdot 100
\end{align*}
\]

where \(GT_{IMT}\) is the average value of the Ground-Truth IMT on the image database (reported by the fourth column of Table IV), whereas \(FOAM_{1IMT}, CALEX_{1IMT}, CARES_{1IMT}, \) and \(CARES_{2IMT}\) are the average values of the four segmentation techniques (as reported by the third column of Table IV). CARES 2.0 was the best performing technique and showed a FoM equal to 96%. CALEX 1.0 showed a FoM of about 91%, CARES 1.0 of about 95%, and FOAM 1.0 of about 89%.

5. DISCUSSION

In this paper we described an improved technique for the automated IMT measurement in carotid ultrasound images. This technique, which we named as CARES 2.0, was optimized for segmentation of the far (distal) wall in carotid longitudinal images. The automated carotid recognition (stage-I) was performed by using an integrated strategy of image feature extraction, fitting, and classification, which proved robust to noise.2,18 The distal wall segmentation (stage-II) was performed by using an improved edge snapper, called FOAM 1.0 operator. The principal novelty of CARES 2.0 resides in: (a) Superior cascaded Stage-I and Stage-II sub-systems by introducing a check for a false far adventitia borders in Stage-I and a bi-directional FOAM in Stage-II; (b) Higher accuracy of CARES 2.0 compared to FOAM 1.0, CALEX 1.0 and CARES 1.0; and (c) Superior reproducibility (precision). We label the improved FOAM to be as
FOAM 2.0, which incorporated heuristic changes leading to a robust bidirectional FOAM. The major differences between the original FOAM 1.0 by Faita et al.\(^3\) and our implementation of FOAM 2.0 are the following:

1. FOAM 1.0 required the tuning of three thresholds, which were called \(\eta_1\), \(\eta_2\), \(\delta_1\) (see Table I on page 1355 of the paper by Faita et al.\(^3\)). \(\eta_1\) and \(\eta_2\) were used to locate the possible LI and MA peaks, respectively. These coefficients are intensity thresholds: a given intensity peak along a column of the image and can be considered as LI candidate if its intensity is higher than the product of \(\eta_1\) with the maximum intensity of that column. Similarly, the MA candidate must have intensity higher than the product of \(\eta_2\) with its maximum intensity. The \(\delta_1\) threshold is used to perform outlier removal. All these thresholds must be re-tuned when the image characteristics change, which is typical case of any multi-institutional databases. Our implementation of FOAM 2.0 does not require any re-tuning or re-definition of these thresholds. We used intensity criteria based on the percentiles of the column intensity distribution. Hence, we only relied on relative thresholds, there by widening the applicability of the FOAM operator.

2. The FOAM 1.0 implementation required an outlier removal stage based on regression analysis. Interpolation and thresholding (as mentioned in the previous point) was used in order to regularize the LI/MA profiles. The FOAM 2.0 used in our strategy used a spike detection and removal stage, which cleaned all the possible glitches in the LI/MA tracings.

3. Our FOAM 2.0 proved to be intrinsically highly stable, because we also introduced a lumen check as a marker which acted as a validation step for our LI/MA border detection. The lumen check was performed by a local statistics approach.\(^2\) Our heuristic search for the LI/MA peaks had been perfectly integrated with the lumen check procedure, thereby avoiding the LI profiles to cross over into the vessel lumen.

Our tests showed that FOAM 1.0 did not reach acceptable performance when used to process our multi-institutional testing database. The IMT measurement accuracy was as low as \(-0.091 \pm 0.161\) mm, a value higher than the current performing methods. To reach optimal performance, FOAM 1.0 must be carefully tuned on the basis of the image characteristics. In our testing dataset, we had images coming from two different Institutions acquired by different sonographers. Therefore, the image characteristics were very inhomogeneous. FOAM 1.0 could not reach the performance published in Faita et al.\(^3\) they found an average IMT bias equal to 0.01 \pm 0.038 mm.

We benchmarked CARES 2.0 against previously developed CALEX 1.0,\(^2\) CARES 1.0,\(^1\) and user-driven FOAM.\(^3\) CARES 2.0 showed an IMT measurement bias equal to \(-0.032 \pm 0.178\) mm, which was better than CALEX 1.0 (0.070 \pm 0.331 mm), FOAM 1.0 (\(-0.091 \pm 0.161\) mm) and CARES 1.0 (0.035 \pm 0.198 mm), respectively. CARES 2.0 showed an IMT measurement bias equal to \(-0.032 \pm 0.178\) mm, which was better than CALEX 1.0 (0.070 \pm 0.331 mm), FOAM 1.0 (\(-0.091 \pm 0.161\) mm) and CARES 1.0 (0.035 \pm 0.198 mm), respectively. Thus CARES 2.0 showed an improvement of 54%
over CALEX 1.0, 65% over stand alone FOAM 1.0 and 9% over CARES 1.0. Compared to CARES 1.0, CARES 2.0 improved the reproducibility by 10%. CARES 2.0 ensured complete automation and increased the reproducibility of the IMT measurement, a step closer for clinical usage.

A better representation of the reproducibility or precision can be seen visually by Bland-Altman plots. Figure 8 shows the Bland-Altman plots for CARES 1.0 (Fig. 8(D)) and CARES 2.0 (Fig. 8(C)). It can be noticed that the standard deviation of the CARES 1.0 estimates is higher than that of CARES 2.0. Therefore, CARES 1.0 has a low reproducibility. Figure 10 compares the scatter diagrams for CARES 1.0 (Fig. 10(A)) with CARES 2.0 (Fig. 10(B)). CARES 2.0 showed a good correlation with GT (correlation coefficient $r = 0.819$), whereas CARES 1.0 showed a poor correlation ($r = 0.344$). The distribution of CARES 1.0 IMT errors is reported by Figure 9(D), that of CARES 2.0 in Figure 9(C). The cumulative frequency (black line) shows that CARES 1.0 has a high dispersion. As we already mentioned, high dispersion of the IMT measurement errors means a low reproducibility and, therefore, a limited clinical applicability.

Figure 11 compares LI/MA profiles for CARES 1.0 (Fig. 11(A)) and CARES 2.0 (Fig. 11(B)). It is possible to notice that CARES 1.0 profiles are inaccurate and affected by spikes and inaccuracies. There are two problems affecting CARES 1.0 LI/MA profiles that have been solved in CARES 2.0. (a) The presence of LI spikes protruding into the vessel lumen. This problem is due to noise. As can be seen that blood backscattering in lumen vessel causes the intensity pixels to have a higher intensity values. The heuristic of FOAM 1.0 (stage-II of CARES 1.0) does not follow the comprehensive protocol for lumen marker and, therefore, the LI profiles are not fully stable. (b) The MA spikes are given by high-intensity points located above the actual MA interface. These spikes are present due to the lack of a spike detection and removal algorithm. CARES 2.0 corrects both these problems and ensures very accurate LI/MA tracings (Fig. 11(B)).

Figure 12 shows the effect of bi-directional of FOAM peak location (now called, FOAM 2.0). Figure 12(A) shows a zoomed portion of the CA distal wall. The white dashed line represents the automatically traced AD$_D$. The AD$_D$ is not actually placed on the adventitia layer, but it has been traced in-between the LI and the MA interfaces. Figure 12(B) shows the LI/MA profiles traced by CARES 1.0. The segmentation is inaccurate, because the MA profile shows incorrect placement. This shows that FOAM 1.0 does not take advantage of the bidirectional nature of FOAM (so called FOAM 1.0). This inaccurate tracing...
Fig. 10. Scatter diagram computer-based IMT (CARES) versus Ground Truth IMT: CARES 1.0 (A), CARES 2.0 (B). The horizontal axis represents the Ground-Truth IMT and the vertical axis represents the estimated IMT values.

Fig. 11. Comparative segmentation of CARES 1.0 versus CARES 2.0: (A) CARES 1.0 segmentation of a B-Mode image. (B) CARES 2.0 segmentation of the same image. The CARES 1.0LI profile is characterized by spikes protruding into the vessel lumen. The CARES 1.0MA profiles present negative direction spikes. CARES 2.0 profiles are optimized and are spike independent.

Fig. 12. (A) ADF profile traced by using Stage-I of refined CALEX 1.0. Note that the ADF profile is not correct, since it is traced in-between the LI and the MA interfaces. (B) Segmentation results from CARES 1.0. The heuristic of CARES 1.0 does not allow for recovering the inaccurate positioning of the ADF; hence, CARES 1.0 segmentation is incorrect. (C) Segmentation results from CARES 2.0. The new bidirectional FOAM heuristic search technique allows for searching maxima under the ADF.
of ADₚ generates an error condition that CARES 1.0 cannot recover. Figure 12(C) shows the segmentation of CARES 2.0. The bi-directional search of FOAM 2.0 allows searching the MA peak below the ADₚ. Therefore, CARES 2.0 can effectively recover the possible sub-optimal tracings of stage-I.

The performance of CARES 2.0 cannot be easily compared to those of other techniques. This for two main reasons: first, most the best performing IMT measurement techniques are semi-automated and, second, other automated techniques were validated on single-institution databases. Overall, the best performing technique, in terms of accuracy, is the original FOAM method proposed by Faita et al., which reached IMT measurement errors equal to about 3%. Being the IMT nominally equal to about 1 mm, Rossi's technique based on the multi-scale anisotropic baricenter (MAB). They obtained an IMT error equal to about 0.01 ± 0.038 mm on their data sets. Stein et al. proposed the most reproducible method we found in literature, which showed IMT measurement error of 0.012 ± 0.006 mm. However, both these methods are semi-automated and require user interaction. With respect to semi-automated techniques, CARES 2.0 has a scope of improvement in both accuracy and reproducibility. However, CARES 2.0 shows a major advancement with respect to CARES 1.0 in terms of reproducibility, which is the criterion for clinical acceptability.

In 2010, Rossi et al. proposed an automated IMT measurement technique based on the multi-scale anisotropic baricenter (MAB). They obtained an IMT error equal to about 3%. Being the IMT nominally equal to about 1 mm, Rossi’s technique had an accuracy of about 0.03 mm. Our CARES 2.0 model shows in concurrence to Rossi et al.’s method. The reproducibility of Rossi et al. technique was equal to 0.05 mm, about three times better than CARES 2.0. It must be noted, however, that the technique by Rossi et al. was tested on phantom images and on a total of 6480 ultrasound carotid images, relative to 36 scans of 12 healthy subjects. Further, the MAB based technique was tested on a single-institution database, on a relative small number of subjects (12 in comparison to 250 subjects used for CARES 2.0). On the contrary, CARES 2.0 was tested on a dataset comprising of both normal and pathologic carotid arteries. We did not implement Rossi’s method hence, comparison could be exactly made. We however believe that there is a potential for further improvement in both Stages-I and II of CARES 2.0, which our team is constantly working on.

6. CONCLUSION

In this paper we showed the architecture and characterization of CARES 2.0, a completely automated technique for IMT measurement in carotid ultrasound imaging. This technique is a major improvement over previously developed automated methods (CALEX 1.03 and CALEX 1.07), both in accuracy and reproducibility of the IMT estimates. The model used two-cascaded stage as a system. The innovation of CARES 2.0 is the adoption of two major break thoughts: (a) spotting and correcting the false far adventitia borders for carotid localization in stage-I; and (b) intelligent heuristic search for the detection of the LI/MA peaks in stage-II. Both stages utilize the lumen as a marker for effect design, while the stage-II incorporates a relative threshold for the peak detection to avoid glitches of the LI profile, and a spike detection and removal algorithm.

The performance assessment of CARES 2.0 was done on a fairly large multi-institutional database, comprising healthy and pathologic arteries. Despite the need for a further improvement in the reproducibility of the estimates, we believe that CARES 2.0 showed encouraging results. We demonstrated that CARES 2.0 model gave an improvement in IMT bias by 54% over CALEX 1.0, 65% over FOAM 1.0 and 9% over CARES 1.0. Compared to CARES 1.0, CARES 2.0 improved the reproducibility by 10% and FoM by about 5%.

CARES 2.0, in its future technological development, will constitute the principal benchmarking technique for assessing the clinical applicability of automated methods. The innovations we brought into CARES 2.0 proved very effective in improving the overall reproducibility.

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References and Notes


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