Volumetric quantification of fibrous caps using intravascular optical coherence tomography

Zhao Wang,1 Daniel Chamie,2 Hiram G. Bezerra,2 Hirosada Yamamoto,2 Jan Kanovsky,2 David L. Wilson,1 Marco A. Costa,2 and Andrew M. Rollins1*

1Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, 44106, USA
2Cardiovascular Imaging Core Laboratory, Harrington Heart & Vascular Institute, University Hospitals Case Medical Center, Cleveland, OH, 44106, USA
*rollins@case.edu

Abstract: The rupture of thin-cap fibroatheroma accounts for most acute coronary events. Optical Coherence Tomography (OCT) allows quantification of fibrous cap (FC) thickness in vivo. Conventional manual analysis, by visually determining the thinnest part of the FC is subject to inter-observer variability and does not capture the 3-D morphology of the FC. We propose and validate a computer-aided method that allows volumetric analysis of FC. The radial FC boundary is semi-automatically segmented using a dynamic programming algorithm. The thickness at every point of the FC boundary, along with 3-D morphology of the FC, can be quantified. The method was validated against three experienced OCT image analysts in 14 lipid-rich lesions. The proposed method may advance our understanding of the mechanisms behind plaque rupture and improve disease management.

© 2012 Optical Society of America

OCIS codes: (100.0100) Image processing; (110.4500) Optical coherence tomography.

References and links
1. V. L. Roger, A. S. Go, D. M. Lloyd-Jones, R. J. Adams, J. D. Berry, T. M. Brown, M. R. Carnethon, S. Dai, G. de Simone, E. S. Ford, C. S. Fox, H. J. Fullerton, C. Gillespie, K. J. Greenland, S. M. Hailpern, J. A. Heit, P. M. Ho, V. J. Howard, B. M. Kissela, S. J. Kittner, D. T. Lackland, J. H. Lichtman, L. D. Lisabeth, D. M. Makuc, G. M. Marcus, A. Marelli, D. B. Matchar, M. M. McDermott, J. B. Meigs, C. S. Moy, D. Mozaffarian, M. E. Mussolino, G. Nichol, N. P. Paynter, W. D. Rosamond, P. D. Sorlie, R. S. Stafford, N. T. Navas, M. B. Turner, N. D. Wong, J. Wylie-Rosett, V. L. Roger, and M. B. Turner; American Heart Association Statistics Committee and Stroke Statistics Subcommittee, “Heart disease and stroke statistics—2011 update: a report from the American Heart Association,” Circulation 123(4), e18–e209 (2011).
2. E. Falk, “Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi,” Br. Heart J. 50(2), 127–134 (1983).
3. R. Virmani, A. P. Burke, F. D. Kolodgie, and A. Farb, “Vulnerable plaque: the pathology of unstable coronary lesions,” J. Interv. Cardiol. 15(6), 439–446 (2002).
4. R. Virmani, F. D. Kolodgie, A. P. Burke, A. Farb, and S. M. Schwartz, “Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions,” Arterioscler. Thromb. Vasc. Biol. 20(5), 1262–1275 (2000).
5. A. P. Burke, A. Farb, G. T. Malcom, Y. H. Liang, J. Smialek, and R. Virmani, “Coronary risk factors and plaque morphology in men with coronary disease who died suddenly,” N. Engl. J. Med. 336(18), 1276–1282 (1997).
6. H. G. Bezerra, M. A. Costa, G. Guagliumi, A. M. Rollins, and D. I. Simon, “Intracoronary optical coherence tomography: a comprehensive review clinical and research applications,” JACC Cardiovasc. Interv. 2(11), 1035–1046 (2009).
7. D. Huang, E. A. Swanson, C. P. Lin, J. S. Schuman, W. G. Stinson, W. Chang, M. R. Hee, T. Flotte, K. Gregory, C. A. Puliafito, and et, “Optical coherence tomography,” Science 254(5035), 1178–1181 (1991).
8. I.-K. Jang, B. E. Bouma, D.-H. Kang, S.-J. Park, S.-W. Park, K.-B. Seung, K.-B. Choi, M. Shishkov, K. Schmedtje, E. Pomerantsev, S. L. Houser, H. T. Aretz, and G. J. Tearney, “Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound,” J. Am. Coll. Cardiol. 39(4), 604–609 (2002).
9. T. Kubo, T. Imanishi, S. Takarada, A. Kuroi, S. Ueno, T. Yamano, T. Tanimoto, Y. Matsuo, T. Masho, H. Kitabata, K. Tsuda, Y. Tomobuchi, and T. Akasaka, “Assessment of culprit lesion morphology in acute
myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angiography,” J. Am. Coll. Cardiol. 50(10), 933–939 (2007).

10. K. Fujii, M. Masutani, T. Okumura, D. Kawasaki, T. Akagami, A. Ezumi, T. Sakoda, T. Masuyama, and M. Ohyanagi, “Frequency and predictor of coronary thin-cap fibroatheroma in patients with acute myocardial infarction and stable angina pectoris a 3-vessel optical coherence tomography study,” J. Am. Coll. Cardiol. 52(9), 787–788 (2008).

11. Y. Ino, T. Kubo, A. Tanaka, A. Kuroi, H. Tsujjoka, H. Ikejima, K. Okouchi, M. Kashiwagi, S. Takarada, H. Kitabata, T. Tanimoto, K. Komukai, K. Ishibashi, K. Hirata, M. Mizukoshi, T. Imanishi, and T. Akasaka, “Difference of culprit lesion morphologies between ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study,” JACC Cardiovasc. Interv. 4(1), 76–82 (2011).

12. M. Kashiwagi, A. Tanaka, H. Kitabata, H. Tsujikoka, H. Matsumoto, Y. Arita, K. Okochi, A. Kuroi, H. Kataiwa, T. Tanimoto, H. Ikejima, S. Takarada, T. Kubo, K. Hirata, N. Nakamura, M. Mizukoshi, T. Imanishi, and T. Akasaka, “Relationship between coronary arterial remodeling, fibrous cap thickness and high-sensitivity C-reactive protein levels in patients with acute coronary syndrome,” Circ. J. 73(7), 1291–1295 (2009).

13. T. Kubo, T. Imanishi, M. Kashiwagi, H. Ikejima, H. Tsujjoka, A. Kuroi, K. Ishibashi, K. Komukai, T. Tanimoto, Y. Amano, T. Tanimoto, S. Takarada, A. Tanaka, M. Mizukoshi, and T. Akasaka, “Multiple coronary lesion instability in patients with acute myocardial infarction as determined by optical coherence tomography,” Am. J. Cardiol. 105(3), 318–322 (2010).

14. S. Rathore, M. Terashima, H. Matsuo, Y. Kinoshita, M. Kimura, E. Tsuchikane, K. Nasu, M. Ebara, Y. Asakura, O. Kato, and T. Suzuki, “In vivo detection of the frequency and distribution of thin-cap fibroatheroma and ruptured plaques in patients with coronary artery disease: an optical coherence tomographic study,” Coron. Artery Dis. 22(1), 64–72 (2011).

15. S. Takarada, T. Imanishi, T. Kubo, T. Tanimoto, H. Kitabata, N. Nakamura, A. Tanaka, M. Mizukoshi, and T. Akasaka, “Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study,” Atherosclerosis 202(2), 49–497 (2009).

16. A. Tanaka, T. Imanishi, H. Kitabata, T. Kubo, S. Takarada, T. Tanimoto, A. Kuroi, H. Tsujijoka, H. Ikejima, S. Ueno, H. Kataiwa, K. Okouchi, M. Kashiwagi, H. Matsumoto, K. Takemoto, N. Nakamura, K. Hirata, M. Mizukoshi, and T. Akasaka, “Morphology of exertion-triggered plaque rupture in patients with acute coronary syndrome: an optical coherence tomography study,” Circulation 118(23), 2368–2373 (2008).

17. T. Yonetsu, T. Kakuta, T. Lee, K. Takahashi, N. Kawaguchi, G. Yamamoto, K. Koura, K. Hisihikari, Y. Jesaka, H. Fujiwara, and M. Isobe, “In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography,” Eur. Heart J. 32(10), 1251–1259 (2011).

18. T. Kume, T. Akasaka, T. Kawamoto, H. Okura, N. Watanabe, E. Toyota, Y. Neishi, R. Sukmawan, Y. Sadahira, and K. Yoshida, “Measurement of the thickness of the fibrous cap by optical coherence tomography,” Am. Heart J. 152(4), 755.e1–755.e4 (2006).

19. H. Yabushita, B. E. Bouna, S. L. Houser, H. T. Aretz, I. K. Jang, K. H. Schlendorf, C. R. Kauffman, M. Shishkov, D. H. Kang, E. F. Halpern, and G. J. Tearney, “Characterization of human atherosclerosis by optical coherence tomography,” Circulation 106(13), 1640–1645 (2002).

20. O. C. Raflf, F. M. Merchant, G. J. Tearney, S. Chia, D. D. Gauthier, E. Pomerantsev, K. Mizuno, B. E. Bouna, and I.-K. Jang, “In vivo association between positive coronary artery remodelling and late coronary plaque characteristics assessed by intravascular optical coherence tomography,” Eur. Heart J. 29(14), 1721–1728 (2008).

21. T. H. Cormen, C. E. Leiserson, R. L. Rivest, and C. Stein, Introduction to Algorithms (MIT Press, 2001).

22. G. van Soest, J. G. Bosch, and A. F. W. van der Steen, “Azimuthal registration of image sequences affected by nonuniform rotation distortion,” IEEE Trans. Inf. Technol. Biomed. 12(3), 348–355 (2008).

23. Z. Wang, H. Kyono, H. Bezerra, D. Wilson, M. Costa, and A. Rollins, “Automatic segmentation of intravascular optical coherence tomography images for facilitating quantitative diagnosis of atherosclerosis,” Proc. SPIE 7889, 78890N (2011).

24. G. van Soest, T. Goderie, E. Regar, S. Koljenovic, G. L. van Leenders, N. Gonzalo, S. van Noorden, T. Okamara, B. E. Bouna, G. J. Tearney, J. W. Oosterhuis, P. W. Serruys, and A. F. van der Steen, “Atherosclerotic tissue characterization in vivo by optical coherence tomography attenuation imaging,” J. Biomed. Opt. 15(1), 011105 (2010).

25. C. Xu, J. M. Schmitt, S. G. Carlier, and R. Virmani, “Characterization of atherosclerosis plaques by measuring both backscattering and attenuation coefficients in optical coherence tomography,” J. Biomed. Opt. 13(3), 034003–034008 (2008).

26. M. S. Nguyen, O. Salvado, D. Roy, G. Steyer, M. E. Stone, R. D. Hoffman, and D. L. Wilson, “Ex vivo characterization of human atherosclerotic fibrous cap plaque components using cryo-imaging,” J. Microsc. 232(3), 432–441 (2008).

27. C. L. Lendon, M. J. Davies, G. V. R. Born, and P. D. Richardson, “Atherosclerotic plaque caps are locally weakened when macrophages density is increased,” Atherosclerosis 87(1), 87–90 (1991).

28. J. Ohayon, G. Finet, A. M. Gharib, D. A. Herza, P. Tracqui, J. Heroux, G. Rioufol, M. S. Kotsy, A. Elagha, and R. Pettigrew, “ Necrotic core thickness and positive arterial remodeling index: emergent biomechanical factors for evaluating the risk of plaque rupture,” Am. J. Physiol. Heart Circ. Physiol. 295(2), H717–H727 (2008).
1. Introduction

Coronary artery disease (CAD) is the most frequent cause of death worldwide. Each year, an estimate of 785,000 Americans will have a new coronary attack, and about 470,000 will have a recurrent event [1]. Most acute coronary events result from rupture of the protective fibrous cap (FC) overlying an atherosclerotic plaque [2]. Thin cap fibroatheroma (TCFA) has been identified as the most frequent precursor lesion that leads to plaque rupture [3]. TCFA has been characterized as a plaque containing a large lipid necrotic core covered by a thin FC infiltrated by macrophages [3,4]. An ex vivo morphometric assessment of 41 ruptured coronary plaques revealed that the mean cap thickness was 23 ± 19 µm and 95% of these FCs measured less than 64 µm [5]. Because of this, a thickness of 65µm has been considered the instability threshold, and thickness of the FC has been considered one of the major morphometric determinants of those plaques prone to rupture [3,4]. Identifying these so-called “vulnerable plaques” before symptoms arise, may allow the adoption of preventive therapeutic measures to avoid subsequent myocardial infarctions and sudden deaths. This largely relies on improvement of imaging technologies that allow better characterization of fibroatheroma in vivo.

Intravascular Optical Coherence Tomography (OCT) is a high resolution (10-20 µm) imaging modality that can image the depth-resolved profile of coronary artery to about 1-2mm [6,7]. OCT has better sensitivity and specificity for detection of lipid plaques as compared to intravascular ultrasound (IVUS) [8] and is currently the only imaging modality that can measure the FC thickness in vivo [9]. OCT has already been used in several in-vivo studies to assess the correlation between the incidence of TCFA/FC thickness and clinical presentations in living patients [10–17].

The current accepted standard method for assessing FC thickness using OCT images is based on single measurements of the thinnest portion of the FC [9,18]. In practice, the segment of interest of the coronary vessel is imaged in 3D using a catheter probe and a pull-back procedure. The image data are subsequently analyzed manually by expert analysts. The cross-sectional image within a field of view encompassing a lipid-rich plaque where the FC thickness appears to be thinnest is visually identified. The OCT criteria for identification of a lipid-rich plaque are the presence of a signal-poor region with diffuse boundaries and high attenuation [19]. In the selected cross section, the thinnest portion of the FC is visually determined and its thickness is manually measured. In order to decrease variability, averaging multiple FC thickness measurements has been proposed [13,20].

However, there are two limitations associated with this method. First, the measured FC thickness is subject to inter-observer variability due to visual uncertainties involved in the entire process. Second, the FC is intrinsically a 3-D structure and single point/single frame measurements are unable to characterize the volumetric nature of FC. Although the thickness of FC has been suggested a risk factor for plaque rupture, the exact mechanisms behind FC thinning and plaque rupture are unknown. A more consistent and comprehensive method for FC quantification may better elucidate the unknown factors associated with plaque rupture. In this paper, we present a new, computer-aided algorithm for semi-automatic volumetric quantification of the FC. With this method, the circumferential distribution of the lipid plaques/FC was first identified by human analysts in all frames containing FC, then the FC boundaries in the radial dimensions were automatically segmented and volumetric quantification was performed on the segmented FC. In the following sections, we first describe how the FC boundaries can be accurately and robustly segmented using a dynamic programming algorithm. We validate the method by comparing its accuracy and variability to that provided by three experienced OCT analysts. To demonstrate the significance of the
method, we assess the intra-observer and inter-observer variability of the conventional single measurement by human analysts. Lastly, we introduce quantitative volumetric metrics that can be derived from the segmentation results.

2. Methods

2.1. Population, image acquisition and study protocol

The population of this study is comprised of 10 elective patients who underwent OCT evaluation of target coronary arteries prior to percutaneous coronary intervention, between September and October 2010. All OCT images were acquired by a commercial Fourier Domain OCT system (C7-XRTM OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota) at University Hospitals at Case Medical Center (Cleveland, OH), digitally stored and de-identified by the Institution’s Cardiovascular Imaging Core Laboratory. The axial resolution of the system is about 15 µm. The scan characteristics of the system are: 50000 lines/s, 504 lines/frame, yielding 100 fps and 20 mm/s pullback speed yielding a 200 µm frame interval. Lipid-rich plaques were selected by an interventional cardiologist experienced in reading OCT images according to the presence of signal-poor regions with diffuse borders under OCT [19]. Calcified plaques may also produce a bright interface overlying a signal-poor region which, opposed to lipid-rich plaques, has a heterogeneous pattern with well-defined sharp boundaries [19], and were excluded from this study. Once the lipid-rich plaque was identified, all of the consecutive frames in the pullback containing the lesion were selected. A total of 323 images from 14 lipid rich lesions were included and used for validation.

2.2. Image analysis method

The OCT raw data were logarithmically compressed and transformed from the polar coordinates (θ, r) to the Cartesian coordinates (x, y) consisting of 1024 by 1024 pixels (pixel size: 9.4 by 9.4 µm). The major steps for volumetric quantification of FC are (1) segmentation of FC boundaries in all frames containing the lesion, and (2) quantification based on the segmentation.

FC is delineated by a luminal boundary and an abluminal boundary. In the non-ruptured plaque the FC protects the underlying lipid/necrotic core from contacting the circulating blood. Therefore, the luminal boundary coincides with the vessel lumen contour. The abluminal boundary is commonly described as the “diffuse border” created by the interface between the FC and the underlying lipid pool. We adopt a sequential approach to first detect the vessel luminal boundary, based on which we can then track the FC abluminal boundary. The lumen contour will also be used for validation and quantification purposes.

Searching for the vessel luminal boundary and FC abluminal boundary in the polar coordinates of OCT images fit the graph search family of optimization problems naturally. The lumen boundary is unique and the accumulated optical intensity difference between the pixels from the vessel and luminal side along the contour is maximum. The FC abluminal boundary is the optimum boundary that best separates the FC from the underlying lipid plaque.

2.2.1. Dynamic programming

Dynamic programming (DP) is a general technique used to solve optimization problems [21]. The basic concept is to find the global optimal solution to the original problem by building on optimum solutions to subproblems. It is very robust in the presence of noise and this is attractive to OCT image analysis because OCT images often suffer from speckle noise and various artifacts. DP has been used previously in intravascular OCT to correct non-uniform rotation distortion [22]. Consider the OCT images in polar coordinates (θ, r) where θ is angle and r is depth. We assign each pixel at row \( i \) and column \( j \) in the OCT image an objective
function \( f(i, j) \) favoring the characteristics of lumen or FC abluminal boundary. Given the starting row (angle) \( \theta_a \) and ending row \( \theta_b \) of the boundary, we are essentially searching a path \( P_{\theta_a \rightarrow \theta_b} \) from \( \theta_a \) to \( \theta_b \) with the optimal cost \( C \). We can break the problem into subproblems such that \( P_{\theta_a \rightarrow \theta_b} \) is always coming from \( P_{\theta_a \rightarrow \theta_b-1} \) with some connectivity constraint. Therefore, we have the following recursive function:

\[
C(i, j) = \max_{j - \Delta j \leq j' \leq j + \Delta j} \left\{ C(i-1, j') + f(i, j) \right\} \quad \theta_a < i \leq \theta_b \\
C(i, j) = f(i, j) \quad i = \theta_a
\]

where \( C(i, j) \) is the accumulated cost from row \( \theta_a \) to point \( (i, j) \), \( f^* \) is adjacent to \( j \), and \( n \) specifies connectivity. The global optimum boundary can be found by selecting the point in row \( \theta_b \) where the accumulated cost is maximum and back tracking the path. Equation (1) defines the common method used for lumen and FC abluminal boundary segmentation. Only the objective function is different for different tasks.

2.2.2. Lumen and guide wire segmentation

The objective function for lumen segmentation can be defined straightforwardly as the pixel value difference between the vessel side and the luminal side:

\[
f_{\text{lumen}}(i, j) = \bar{T}(i, j) - \bar{T}(i, j - m_l < j_a < j)
\]

where \( \bar{T} \) refers to the average of pixel value, and \( m_v \) and \( m_l \) are the length of windows on the vessel and luminal side, respectively. In this study, we chose \( m_v = m_l = 0.1 \text{ mm} \). Under this definition, pixels of the guide wire reflections may obscure the lumen boundary and need to be excluded from lumen segmentation. We have proposed a guide wire segmentation method that is able to extract the global optimum guide wire positions of all the frames in the entire pullback at once [23]. Briefly, a 2D longitudinal image of average \( A \) line values plotted as a function of frame number and \( \theta \) is created (Fig. 1(b)). The regions of guide wire shadow become a continuous dark band. Similar to lumen segmentation, an objective function of pixel value difference is applied to the two boundaries of the dark band, but with different signs. DP is then applied twice to find the two boundaries.

2.2.3. FC abluminal boundary determination

Although OCT has been suggested to have the ability to quantify FC thickness accurately [18], a quantitative definition of the FC abluminal boundary under OCT has not been proposed. The FC abluminal boundary is usually characterized by a gradual transition of pixel intensity from bright to dark, and visual determination of the optimal transition point can be cumbersome, inaccurate and subject to high variability. On the other hand, given an objective function favoring the appropriate properties of FC, computers can objectively identify the location of the abluminal boundary more consistently than humans. The FC has been defined histologically as a distinct layer of connective tissue covering the lipid core, and consists purely of smooth muscle cells in a collagenous-proteoglycan matrix, with varying degrees of infiltration by macrophages and lymphocytes [4]. The fibrous tissue appears bright by OCT and has a low attenuation coefficient, whereas the lipid pool appears dark and strongly attenuates the light [24,25]. Therefore, we suggest that the FC abluminal boundary has a high intensity difference between the FC and lipid pool, and also a high gradient. Hence, we define the following objective function:

\[
f_{\text{FC}}(i, j) = \bar{T}(i, j - d_i \leq j_a \leq j) - \bar{T}(i, j < j_a \leq j_a) - \lambda \mu
\]
where $d_j$ and $d_{\text{max}}$ are predefined depths to calculate pixel intensity difference, $\mu$ is the slope of pixel value attenuation extracted from the A line segment of length $L$ across $(i,j)$, and $\lambda$ is a weighting term. The parameter values $d_j = 75 \, \mu m$, $d_{\text{max}} = 0.38 \, mm$, $\lambda = 7$, and $L = 38 \, \mu m$ used in the validation set were determined experimentally using a separate training data set ($n = 3$) different from the 14 lesions selected for validation. The ROI for analysis is bounded in the radial dimension by the previously segmented lumen boundary and a predefined maximum depth $d_{\text{max}}$, and in the circumferential dimension by a user-defined starting and ending angle encompassing the selected lesion.

2.2.4. Volumetric quantification

With the fully segmented FC, we can quantify the thickness at each point of the FC luminal boundary, defined as the minimum distance from this point to the FC abluminal boundary. The conventional metric, the minimum FC thickness (MCT), of a single lesion can be simply found by searching for the minimum thickness out of all the points on the FC luminal boundary in all consecutive frames covering this lesion. The mean FC thickness (MeanCT) of a lesion is the average thickness of all points on the FC luminal boundary.

In addition, volumetric metrics of the FC can be defined as follows. The FC surface area (SA) of a lesion can be calculated as the product of the frame interval and the arc length of FC summed over involved frames. The arc length can be determined from the radius of FC luminal boundary with reference to the centroid of the lumen. The absolute and fractional FC categorical surface area (ACSA and FCSA) of a lesion can be calculated as the absolute and relative FC area in a thickness category. In this study, we classified FC thickness into 3 categories: $<65 \, \mu m$, 65-150 $\mu m$ and $>150 \, \mu m$. This definition is based on both pathology studies and in vivo clinical studies using OCT [4,17]. However, further evaluation of the significance of these cut-off values will be important in the future. FC volume (Vol) of a
lesion is calculated from cross sectional FC areas in individual frames using Simpson’s rule. 
*FC volume density* (VD) of a lesion is the FC volume normalized by the lesion length. *FC fractional luminal area* (FLA) is defined as the percentage of luminal area occupied by the FC. *Categorical FC fractional luminal area* (CFLA) is defined in a similar way but only counting the FC area in a thickness category. Cross correlation between the volumetric metrics will be used to evaluate redundancy (collinearity).

### 2.3. Validation experiment

Three experienced OCT analysts were involved in the validation experiments. A graphical user interface written in MATLAB (MathWorks, Inc) and C++ for visualizing and analyzing OCT images was developed and provided to the analysts. Importantly, proper calibration of all OCT image runs through adjustment of the Z-offset [6] was performed by a single operator, and kept the same by the other two analysts and by the computer algorithm. Likewise, the same operator was responsible for selecting all lipid-rich lesions included in the analysis.

In order to allow a comprehensive understanding of the importance of a full volumetric segmentation of the FC, inter-observer variability of FC thickness quantification of all 14 lesions were initially determined by the single-frame, single-measurement concept among the three analysts. In this process, each analyst independently selected the image frame where they suspected the FC was thinnest and determined the FC thickness by a single measurement.

Subsequently, all 323 cross-sectional images from the same 14 lipid-rich lesions were manually segmented by analyst 1 and by the computer algorithm. The accuracy of the computer algorithm was evaluated by comparison with the manual segmentation. In order to assess intra-observer variability, all images were re-analyzed by operator 1 two weeks later. To assess inter-observer variability of manual segmentation of FC boundaries, 50 randomly selected cross-sections were analyzed by operators 2 and 3. At all times, each analyst was blinded to the analysis results performed by the other analysts and the computer algorithm. Only the common region of FC selected by all three analysts was used for comparison. If the FC was blocked by the guide wire shadow, only the shadowed region was excluded for validation.

Since the algorithm determines both the luminal and abluminal boundaries of FC, we evaluated the accuracy of every point on the two boundaries as illustrated in Fig. 2. If we project n rays from the lumen centroid to the FC at one degree intervals, and define the distance from the lumen centroid to the FC luminal and abluminal boundary along ray i as $d_{LB_i}$ and $d_{ALB_i}$, respectively, we can use the mean absolute difference (MAD) between these distances determined from the semi-automatic method and manual segmentation to assess the agreement:

![Fig. 2. Methodology for validation of fibrous cap luminal and abluminal boundary determination. The distance from the two boundaries to the lumen centroid was defined as $d_{LB_i}$ and $d_{ALB_i}$, respectively, and compared between the computer algorithm and human analysts. This distance was calculated along rays at intervals of one degree.](image-url)
\[ \text{MAD}_{LB} = \frac{1}{n} \sum_{i=1}^{n} |d_{LB}^{\text{Manual}} - d_{LB}^{\text{Auto}}| \quad \text{MAD}_{ALB} = \frac{1}{n} \sum_{i=1}^{n} |d_{ALB}^{\text{Manual}} - d_{ALB}^{\text{Auto}}| \]  

The mean signed differences (MSD) can be similarly defined. This stringent metric allows complete comparison of every point on the FC boundary.

3. Results

3.1. Intra- and inter-observer variability of human analysts

3.1.1. Single-point measurement of minimum cap thickness

The intra-observer variability in determining the minimum cap thickness (MCT) was 14.5 ± 11.7 µm for analyst 1. Figure 3 illustrates the manually measured MCT by the three analysts. The concordance correlation coefficient (CCC) of the frame selection was excellent (ccc = 0.9958) among the three analysts, with a mean absolute difference of the selected frame for assessing the MCT of 3.1 ± 4.1 frames. However, the mean absolute difference between the three analysts in assessing the MCT of the 14 lesions was 12.8 ± 8.2 µm, with a very poor CCC (ccc = 0.2450). Of note, when the cut-off point of 65 µm was used to define a TCFA, agreement among all three analysts was reached in only four lesions and at least one analyst held a different assessment in 10 out of the 14 lesions.

![Frame Difference against Analyst 1](a)

![Fibrous Cap Thickness (µm)](b)

Fig. 3. Manual measurements of the minimum cap thickness of the 14 lesions by the three analysts. (a): The difference of the selected frame for measuring the minimum cap thickness by the three analysts was plotted vs. the lesion number. The frame difference is against analyst 1. Frame difference of 0 indicates no difference. (b): The minimum cap thickness measured on the selected frame in (a). CCC: concordance correlation coefficient. CCC<0.4 is considered to be poor agreement. Dashed line: conventional cut-off value of 65 µm for definition of TCFA. Under this definition, one of the three analysts held a different assessment of TCFA for 10 out of 14 lesions.

3.1.2. Manual segmentation of FC

The Mean Absolute Difference (MAD) of the segmentation performed by human analyst 1 in two different time points was 20.7 ± 11.3 µm. The MAD between the three human analysts was 30.3 ± 27.3 µm. The angular difference of the selected circumferential distribution of FC for the three analysts was 9.6 ± 9.9 degrees for all lesions except for one outlier (63.0 degrees).

3.2. Performance of the algorithm

The average processing time for lumen segmentation, guide wire segmentation and FC abluminal boundary determination in a single frame was 0.4s, 0.07s and 0.2-0.4s, respectively (with a duo core 2.00GHz CPU).
The MAD of the FC thickness between the algorithm and analyst 1 in assessing all the 323 images was 27.3 ± 26.7 µm. The MAD of the luminal and abluminal boundary was 15.7 ± 23.4 µm and 25.3 ± 31.4 µm, respectively. The Mean Signed Difference (MSD) of the FC thickness, luminal and abluminal boundary between the algorithm and analyst 1 was 2.9 ± 38.0 µm, 6.0 ± 27.5 µm and −3.2 ± 40.2 µm, respectively.

Figure 4 shows the MAD and MSD comparison of the localization of the luminal and abluminal boundaries and the thickness of the FC by the algorithm and by the three analysts. The MAD between the algorithm and analysts was comparable to that between analysts. The MAD for luminal boundary was less than that for the abluminal boundary. From the MSD results in Fig. 4(b), the bias is around one pixel or less, except between analyst 3 and the algorithm and between analyst 3 and the other two analysts in determining the FC abluminal boundary (and consequently the FC thickness).

Figure 5 illustrates a typical example where the semi-automatically determined contour was very similar to all three analysts. While the analysts tended to smooth the FC boundary, the algorithm exactly followed the border where the intensity difference and gradient were high. Figure 6 shows an example where the algorithm shows disagreement with the three analysts. Compared to the algorithm determined segmentation, the FC traced by analyst 2 is significantly thinner, whereas the one traced by analyst 3 around 9-10 o’clock is thicker.
3.3. Volumetric metrics vs. minimum cap thickness

Among the 14 lesions, there was low correlation between all the volumetric metrics and the conventional metric MCT (Table 1). This indicates that these volumetric metrics characterize independent morphological information about FC. Between the volumetric metrics, there was moderate correlation between ACSA (<65 µm) and MeanCT \( (R = -0.67, p<0.01) \), between FCSA (<65 µm) and MeanCT \( (R = -0.76, p<0.01) \), between CFLA (<65 µm) and MeanCT
(R = −0.65, p<0.01), between ACSA (<65 µm) and SA(R = 0.74, p<0.01), between ACSA (<65 µm) and Vol (R = 0.64, p<0.01), between FLA (<65 µm) and SA (R = 0.64, p<0.01), between VD and SA (R = 0.77, p<0.01), between VD and FLA (R = 0.77, p<0.001), and between VD and Vol (R = 0.82, p<0.001). There was strong correlation between Vol and SA (r = 0.99, p<0.0001).

3.4. Three dimensional visualization of FC

The segmented FC can be visualized in 3D with a continuous colormap, from blue to green to red, indicating the FC thickness ranging from 300 µm to one pixel length. Figure 7 illustrates 2 cases, both with TCFA, with FC thickness rendered in 3D. If assessed using only the conventional methodology, the morphological differences between the cases would not be apparent. However, the 3-D visualization demonstrates dramatically different characteristics. In particular, the vessel shown in the lower panel has a significantly higher fraction of thin FC as compared to the one in the upper panel.

| Table 1. Correlation coefficients between the volumetric metrics in 14 lesions$^a$ |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | MCT             | MeanCT          | ACSA (<65 µm)   | FCSA (<65 µm)   | SA              | FLA             | CFLA (<65 µm)   | Vol             |
| VD              | 0.02            | 0.18            | 0.35            | −0.49           | 0.77**          | 0.77**          | −0.26           | 0.82**          |
| Vol             | −0.31           | −0.14           | 0.64*           | −0.30           | 0.99***         | 0.63            | 0.08            |
| CFLA (<65 µm)   | −0.23           | −0.65*          | 0.39            | 0.47            | 0.17            | 0.11            |
| FLA             | 0.04            | −0.11           | 0.45            | −0.28           | 0.64*           |
| SA              | −0.37           | −0.27           | 0.74*           | −0.19           |
| FCSA (<65 µm)   | −0.20           | −0.76*          | 0.44            |
| ACSA (<65 µm)   | −0.49           | −0.67*          |
| MeanCT          | 0.34            |

$^a$Significance levels: *p<0.01, **p<0.001, ***p<0.0001.

4. Discussion

4.1. Minimum cap thickness

A fibrous cap (FC) with the minimum cap thickness <65 µm has been used as the threshold to characterize TCFA by histopathology [4], but no causal relationship can be derived for prediction of plaque rupture. While largely accepted, the determination of this value may be affected by artifacts from histology preparation such as tissue shrinkage, and selection bias (this cut-off was derived from plaques that had already ruptured). A recent OCT study on 266 lesions suggested that 80 µm might be the critical cap thickness that may confer instability to a coronary plaque in living patients [17]. However, OCT and pathology studies were based on single or multiple individual FC measurements and significant variations can be expected, as shown in the present study (Fig. 3). The MAD of 12.8 ± 8.2 µm among the three analysts was actually below the resolution of the OCT system. However, the reported incidence of TCFA can differ dramatically if 65 µm was chosen as the single threshold (Fig. 3(b)). One particular challenge for human analysts is to identify the particular frame containing the cap with the minimum thickness. In this study, while the three analysts chose the same frame for most of the lesions, the difference in selection of the site to measure the minimum FC thickness could be substantial for some lesions (e.g. lesion 2 in Fig. 3(a)). The computer-aided method tested...
in this study provides semi-automatic segmentation of the whole FC, which eliminates the uncertainty associated with manual analysis and image selection and allows more accurate determination of the true minimum FC thickness.

![Image of coronary arteries with fibrous caps rendered in a continuous color map indicating the thickness. Both of the two lesions contain TCFA (red arrows) and similar minimum cap thickness. However, the one shown in the lower panel contains a significantly larger surface area with thin cap as compared to the one in the upper panel.]

**Fig. 7.** Two coronary arteries used in the validation study with fibrous caps (FC) rendered in a continuous color map indicating the thickness. Both of the two lesions contain TCFA (red arrows) and similar minimum cap thickness. However, the one shown in the lower panel contains a significantly larger surface area with thin cap as compared to the one in the upper panel.

### 4.2. Do we know the true FC thickness?

Xu et al. [25] has found that lipid plaques have higher backscattering coefficient as compared to FC. Therefore, the study suggested that the true FC boundary is actually within the signal-rich region. If this is true, the FC boundary may precede the steepest decline, and both human analysts and our method may overestimate the FC thickness slightly. However, direct search for the true boundary as a local peak may not be straightforward for human analysts or for algorithms. In clinical images, such peaks are not always present, and even when present, are not readily discernible from surrounding speckle noises. In addition, the presence of macrophages can also cause very strong peak signals. In comparison, searching the maximum gradient and intensity difference to represent the boundary is relatively robust and consistent, which is more important clinically than a slight bias. We will perform further validation studies to confirm the true FC location. As tissue shrinkage and the difficulty for precise registration associated with histology may make it difficult for such validation, a volumetric validation method using Cryo-imaging [26] that gives better registration may be used. If appropriate, an offset value may be added in the model to compensate for the bias.
4.3. Volumetric quantification

A fundamental limitation of the single number description of the FC thickness is the lack of appreciation for the 3-D morphology of FC. While the mechanisms associated with FC rupture remain elusive, it is possible that mechanical stability of the cap may not only depend on the focal point thickness, but also on the thickness of non-focal regions. Moreover, plaque rupture may not necessarily happen at the thinnest part of the FC. These unknown morphological and mechanical properties that ultimately lead to plaque rupture can now be investigated in future studies with the help of the volumetric quantitative method.

Among the volumetric metrics, the FC surface area in a certain thickness category reveals the component of the FC in a certain thickness range. One may speculate that a FC with a larger area of thickness<65 µm may be more vulnerable than a FC with a smaller area of thickness<65 µm. The total and categorical FC fractional luminal area is more precise than using the number of quadrants to represent the distribution of lipid-rich plaques. The FC volume is strongly correlated with the FC surface area. This is not surprising because both metrics depends more on the lesion length rather than the lesion thickness due to the large frame interval (200 µm) of the current OCT system. We could speculate that vulnerability increases with surface area and decreases with thickness, so volume may be less sensitive than surface area even though it includes more information.

![Images of OCT scans with annotations]

Fig. 8. In this case, the computer algorithm mistakenly identified luminal blood as part of the tissue due to the contact between the blood and lumen boundary. In the blood-free region, the algorithm accurately segmented the boundary as compared to human analysts.

4.4. Performance and potential limitations of the method

The semi-automatic method is as accurate as expert analysts (Fig. 4). It is highly robust (global optimum nature of dynamic programming) and fast enough (<1s for single frame) to be used in practice.

One limitation of the semi-automatic method is the inaccurate segmentation of the luminal boundary in presence of luminal blood (Fig. 8). In this study, only one lesion had residual luminal blood. For validation purposes, no manual correction was performed in this study. However, in practice, users could make necessary corrections in such cases.

The current method is semi-automatic because the circumferential boundaries of a FC were defined manually by the analysts. Automated detection of the circumferential boundaries...
is challenging because validated (or at least reproducible) criteria for the FC circumferential boundaries in OCT images have not been defined.

The metrics provided in this study only characterize the morphology of the FC. However, the vulnerability of the FC also depends on inflammation (macrophages) within the FC [27] and other factors in addition to FC thickness. For example, Ohayon et al. [28] has demonstrated that plaque instability is affected by a combination of cap thickness, necrotic core thickness and the arterial remodeling index. The direction of blood flow towards the FC may also affect the vulnerability [11]. Microcalcification within the thin fibrous cap has also been suggested to cause stress-induced plaque rupture [29].

5. Conclusion

We have demonstrated a computer-aided method that is able to segment the boundaries and quantify the 3-D morphology of fibrous caps. The volumetric metrics provide complimentary information to the conventional metric (minimum cap thickness). The method is fast, accurate and robust, and can be used in future studies for more comprehensive characterization of fibrous caps and correlate with clinical presentations to advance our understanding of the mechanisms leading to plaque rupture.

Acknowledgments

The authors would like to thank David Prabbu for his help with 3D visualization, and the reviewers for valuable suggestions on the paper. This project was supported in part by National Institutes of Health grants R21 HL108263 and R01 HL095717 and in part by the American Heart Association predoctoral fellowship (#11PRE7320034).