Diagnosis of Thin-Capped Fibroatheromas in Intravascular Optical Coherence Tomography Images

Effects of Light Scattering

Jennifer E. Phipps, PhD; Taylor Hoyt, BA; Deborah Vela, MD; Tianyi Wang, PhD; Joel E. Michalek, PhD; L. Maximilian Buja, MD; Ik-Kyung Jang, MD, PhD; Thomas E. Milner, PhD; Marc D. Feldman, MD

Background— Intravascular optical coherence tomography (IVOCT) images are recorded by detecting light backscattered within coronary arteries. We hypothesize that non–thin-capped fibroatheroma (TCFA) causes may scatter light to create the false appearance of IVOCT TCFA.

Methods and Results— Ten human cadaver hearts were imaged with IVOCT (n=14 coronary arteries). IVOCT and histological TCFA images were coregistered and compared. Of 21 IVOCT TCFA (fibrous cap <65 µm, lipid arc >1 quadrant), only 8 were true histological TCFA. Foam cell infiltration was responsible for 70% of false IVOCT TCFA and caused both thick-capped fibroatheromas to appear as TCFA, and the appearance of TCFA when no lipid core was present. Other false IVOCT TCFA causes included smooth muscle cell–rich fibrous tissue (12%) and loose connective tissue (9%). If the lipid arc >1 quadrant (obtuse) criterion was disregarded, 45 IVOCT TCFA were identified, and sensitivity of IVOCT TCFA detection increased from 63% to 87%, and specificity remained high at 92%.

Conclusions— We demonstrate that IVOCT can exhibit 87% (95% CI, 75%–93%) sensitivity and 92% specificity (95% CI, 86%–96%) to detect all lipid arcs (both obtuse and acute, <1 quadrant) TCFA, and we also propose new mechanisms involving light scattering that explain why other plaque components can masquerade as TCFA and cause low positive predictive value of IVOCT for TCFA detection (47% for obtuse lipid arcs). Disregarding the lipid arc >1 quadrant requirement enhances the ability of IVOCT to detect TCFA.

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Key Words: atherosclerosis ◼ lipids ◼ myocytes, smooth muscle ◼ plaque, amyloid ◼ tomography, optical coherence

Plaque rupture is responsible for up to 75% of acute coronary syndromes and is an important mechanism for atherosclerotic disease progression. Plaque rupture is most often preceded by the development of a thin-capped fibroatheroma (TCFA), the most common type of vulnerable plaque. Intravascular optical coherence tomography (IVOCT) is the only coronary imaging modality available clinically that has sufficient resolution to identify the thin fibrous cap of a TCFA (<65 µm) overlaying a large lipid core. Although some studies have shown that IVOCT is accurate for imaging TCFA, other studies have reported the false identification of TCFA with IVOCT. Two studies with histological validation have been reported that describe superficial foam cell infiltration that causes strong light attenuation and appears as a lipid pool or TCFA. Another known mechanism for the false appearance of TCFA is tangential light dropout, which occurs when light emitted from the IVOCT catheter propagates tangential to the luminal wall. Similarly, Manfrini et al demonstrated in ex vivo human hearts that only 45% of fibrous cap atheromas were correctly identified by IVOCT because of either low IVOCT signal penetration depth or the inability to distinguish calcium deposits from lipid. Finally, Fujii et al recently reported only 41% positive predictive value (PPV) of IVOCT for TCFA identification. These studies suggest the need for a more comprehensive histological validation of IVOCT identification of TCFA.

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WHAT IS KNOWN

• Intravascular optical coherence tomography (IVOCT) is the only clinical technique capable of imaging the thin fibrous cap of the thin-capped fibroatheroma (TCFA), but image artifacts can cause IVOCT images to falsely appear as TCFAs, such as superficial macrophage infiltration and tangential light dropout.

WHAT THE STUDY ADDS

• This study characterizes intramural components that cause IVOCT images to falsely display TCFAs, the absence of which is proven by rigorous histological analysis and proposes new light-scattering mechanisms for the appearance of these false-positives.

• We demonstrate that IVOCT can exhibit 85% sensitivity and 93% specificity for identification of TCFA and also explain the low positive predictive value for IVOCT TCFA detection in our own study, consistent with others in the literature.

• In a cohort of n=14 human coronary arteries, we quantify the frequency of several false TCFA causes that include superficial macrophages, tangential light dropout, loose connective tissue, punctate foam cells, and smooth muscle cell infiltration of the fibrous cap.

• Sensitivity for IVOCT TCFA detection can be increased if lipid arc lengths <1 quadrant are also considered TCFA; however, because this decreases further the positive predictive value and specificity of IVOCT TCFA detection, we suggest that IVOCT TCFA definitions should be further studied and clarified, perhaps even with the addition of new imaging modalities more specific to the presence of lipid in the arteries, such as fluorescence lifetime imaging or 2-photon luminescence.

light. Thus, one may hypothesize that other constituents of atherosclerotic plaque aside from lipid or necrotic cores may result in decreased light amplitude returning to the IVOCT catheter and false appearance of a TCFA. To test our hypothesis, we performed a histological study to identify false IVOCT TCFA causes and the corresponding light-scattering mechanisms.

Methods

Specimens

Ten human hearts (3 women and 7 men) were acquired through the Southwest Blood & Tissue Center and examined within 24 hours of death. The average age at death was 65±11 years. Six deaths were cardiac related including 4 acute myocardial infarctions. One death was caused by a cerebrovascular event. Evidence of plaque rupture and thrombus was found by both IVOCT and histology in 5 patients. We imaged 14 coronary arteries (n=10 left anterior descending artery [LAD] and n=4 right coronary artery). The Institutional Review Board at the University of Texas approved this study.

Imaging Procedure

A human heart catheterization laboratory was recreated with a custom IVOCT system (Volcano Corporation, San Diego, CA) as reported previously. Briefly, a 1310-nm swept source laser was used to image the LAD and right coronary artery (80-mm pullbacks recorded by 300 IVOCT images). Left and right coronary 6F guide catheters were sewn into the coronary ostia, 0.014” guidewire access to the coronary arteries was gained under fluoroscopic guidance, and a metallic stent was deployed 80 mm from the guide catheter tip as a fiduciary marker. The tissue was maintained at 37°C with a custom-designed imaging chamber. After imaging, the right coronary artery and LAD were perfusion fixed with 10% neutral-buffered formalin at 100 mm Hg. The left circumflex artery was not imaged because of its tortuosity in the ex vivo heart.
Histology
The LADs and right coronary arteries were dissected and processed routinely for histology as in a previous study.11 Tissue was decalcified overnight with Cal-Rite (Richard Allen Scientific) if necessary. The arteries were sliced into 2- to 3-mm-thick rings and further processed for standard paraffin-embedded sections. An average of 25 rings was generated from each artery. Serial tissue sections (5-μm thick) were cut at 120-μm intervals and stained with hematoxylin and eosin, modified Movat pentachrome, and Von Kossa. Anti-CD68 (Dako North America, Inc, Carpinteria, CA) and anti–α-SMC and smooth muscle actin (Sigma-Aldrich, St. Louis, MO) antibodies were used in immunohistochemical studies to identify macrophages and SMCs, respectively.

IVOCT and Histology Coregistration
Each histological ring was matched to a respective IVOCT image as detailed previously.11 Coregistration was performed between IVOCT images and histological sections on the basis of (1) 2 fiducial landmarks (the sewn-in guide catheter and a distally deployed stent, marking the at the proximal and distal ends of the pullback, respectively) that were visible in IVOCT images, fluoroscopy, and radiography before histopathologic processing; (2) a mathematical calculation based on the physical position of IVOCT images in the pullbacks measured against the estimated distance in microns from the fiducial landmarks in the tissue sections; and (3) anatomic landmarks (eg, arterial branches or calcification patterns) and luminal geometric features when present. Two researchers independently coregistered recorded IVOCT images and histological sections, and any discrepancies were reexamined until agreement between coregistrations was obtained.

TCFA and Thick-Capped Fibroatheroma Categories
TCFAs and thick-capped fibroatheroma (ThCFAs) were identified by fibrous cap thickness (<65 or >65 μm, respectively). TCFAs were categorized by IVOCT as acute or obtuse by lipid arc <1 or >1 quadrant, respectively. The lipid arc was measured from the center of the lumen in the IVOCT image. Image segments of all 18 obtuse IVOCT TCFA and 18 non-IVOCT TCFA image segments randomly selected from the University of Texas Health Science Center San Antonio (UTHSCSA) data set were mixed together and sent for external review at an independent IVOCT core laboratory (Massachusetts General Hospital [MGH]), which was blinded to the histology. Two experts in coronary artery pathology evaluated all histology sections. κ coefficients of inter-rater reliability were calculated for both of the previous analyses. Figure 2 describes the categorization of the 5 types of lesions identified in this study: true TCFA, ThCFA identified as TCFA (by IVOCT), true ThCFA, false TCFA, and false ThCFA.

Light-Scattering Mechanisms
To identify additional IVOCT light-scattering mechanisms that resulted in the false appearance of lipid, IVOCT images that had fibrous caps <65 μm and lipid arcs of any length were included in our analysis. The current IVOCT working group consensus document3 does not define IVOCT TCFA based on the lipid arc and accepts lipid arcs <1 quadrant.

Table 1. IVOCT and Histology Measurements of Obtuse OCT TCFA (Lipid Arc >1 Quadrant)

<table>
<thead>
<tr>
<th>TCFA Group</th>
<th>TCFA Length, mm</th>
<th>Fibrous Cap Thickness, μm</th>
<th>Lipid Pool Arc, degrees</th>
</tr>
</thead>
<tbody>
<tr>
<td>True TCFA</td>
<td>8</td>
<td>7±4</td>
<td>23±21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12±11</td>
<td>165±58</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>8</td>
<td>165±58</td>
</tr>
<tr>
<td>ThCFA as TCFA</td>
<td>3</td>
<td>3±1</td>
<td>37±21</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>116±12</td>
<td>169±22</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>116±29</td>
<td></td>
</tr>
<tr>
<td>False TCFA</td>
<td>7</td>
<td>6±4</td>
<td>36±11</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>116±26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>115 (108, 120)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>77 (51, 164)</td>
<td></td>
</tr>
</tbody>
</table>

IVOCT indicates intravascular optical coherence tomography; NA, not applicable; TCFA, thin-capped fibroatheroma; and ThCFA, thick-capped fibroatheroma.
Statistical Methods

Sensitivity, specificity, PPV, and negative predictive value and their 95% confidence intervals were calculated by frame by assigning each IVOCT frame a value of true-positive, true-negative, false-positive, or false-negative. Continuously distributed outcomes are summarized as mean ±1 SD. Estimates and confidence intervals for sensitivity, specificity, PPV, and negative predictive value were based on generalized estimating equation models with a logit link and adjustment for repeated measurements within subject using SAS version 9.4 (SAS Institute, Cary, NC). TCFA were categorized by lipid arc: (1) obtuse and (2) all (acute and obtuse). Statistical data were generated for both categories of TCFA.

Results

IVOCT TCFA

A total of 18 obtuse IVOCT TCFA were identified: 8 (44%) were true TCFA, 3 (17%) were ThCFA that appeared as TCFA, and 7 (39%) were false TCFA. Length, fibrous cap thickness, and lipid pool arc are summarized by IVOCT TCFA (true TCFA, ThCFA as TCFA, and false TCFA) in Table 1. Figure 3 demonstrates an example of a lesion characterized as a true TCFA. False TCFA were caused by many etiologies (Table 2) including clusters of foam cells (Figure 4) and loose connective tissue (Figure 5).

Light-Scattering Mechanisms

Sixty-three IVOCT fibroatheromas (45 IVOCT TCFA and 18 IVOCT ThCFAs) of any lipid arc angle (obtuse and acute) were included for analysis. A total of 45 IVOCT TCFA were identified: 12 (27%) were true TCFA, 8 (18%) were ThCFA that appeared as TCFA, and 25 (56%) were false TCFA. A total of 18 IVOCT ThCFAs were identified: 9 (50%) were true ThCFA and 9 (50%) were false ThCFA. The histological causes associated with each true or false IVOCT TCFA or IVOCT ThCFA are summarized in Table 3. Examples of false TCFA include hypocellular and proteoglycan-rich regions (Figure 6), SMC-rich fibrous tissue (Figure 7), and a calcified nodule (Figure 8).

Accuracy

Sensitivity, specificity, PPV, and negative predictive value for IVOCT TCFA detection are summarized in Tables 4 and 5.

Table 2. Causes of Light Scattering for the Appearance of Obtuse OCT TCFA (Lipid Arc >1 Quadrant)

<table>
<thead>
<tr>
<th>Type 1 causes in fibrous tissue*</th>
<th>TCFA</th>
<th>ThCFA as TCFA</th>
<th>False TCFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Punctate foam cells</td>
<td>...</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>SMC rich</td>
<td>...</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Type 2 causes*  

| Necrotic or lipid core (2-A)   | 8    | ... | ... |
| Clustered foam cells (2-B)     | ...  | 0   | 3   |
| Loose connective tissue (2-C)  | ...  | 0   | 1   |

IVOCT imaging artifacts

| Tangential light dropout       | ...  | 1   | 0   |

IVOCT indicates intravascular optical coherence tomography; SMC, smooth muscle cell; TCFA, thin-capped fibroatheroma; and ThCFA, thick-capped fibroatheroma.

*See Figure 1.
5 by lipid arc (all and obtuse). Sensitivity was numerically increased for all angles relative to obtuse (all 87% and obtuse 63%) and specificities were similar (all 92% and obtuse 96%), whereas PPV was decreased for all angles relative to obtuse (all 37% and obtuse 47%) and negative predictive values were similar (all 99% and obtuse 98%). The $\kappa$ coefficient for

Figure 4. Superficial clustered foam cells caused a false intravascular optical coherence tomography (IVOCT) thin-capped fibroatheroma (TCFA; type 2-B light scattering). IVOCT image with false IVOCT TCFA outlined in red dashes (A). CD68 immunohistochemistry (B) shows that a long superficial cluster of foam cells inside the red dashed circle are responsible for the increased light scattering that causes the appearance of the TCFA in A. Hematoxylin-eosin stain (C), $\alpha$-smooth muscle actin immunohistochemistry (D). Scale bars, 1 mm.

Figure 5. Loose connective tissue caused a false intravascular optical coherence tomography (IVOCT) thin-capped fibroatheroma (TCFA; type 2 light scattering). IVOCT image with false TCFA outlined with red dashes (A). Hematoxylin-eosin stain shows loose connective tissue and ground substance is responsible for the increased light scattering in this region (B). CD68 immunohistochemistry is negative for macrophages (C). Movat pentachrome stain shows loose collagen in the region of interest (D). Scale bars, 1 mm.
the inter-rater reliability test between the 2 IVOCT corelabs (MGH and UTHSCSA) for how well the classifications of TCFA and non-TCFA agreed in the 36 segments of IVOCT images was 0.83 with 95% confidence interval 0.66 to 1.0. The \( \kappa \) coefficient for how well the 2 expert pathologists agreed in their assessment of the histology classification of TCFA was 0.82 with 95% confidence interval of 0.70 to 0.95. Any discrepancies between IVOCT corelabs or pathologists were solved by consensus agreement.

### Discussion

New mechanisms for the appearance of false IVOCT TCFA are identified including SMCs in the fibrous cap and loose connective tissue being mistaken for the lipid core. Foam cell accumulation in the fibrous cap has previously been reported to cause the appearance of false TCFA.\(^3,\,7,\,8,\,10\) Newly described are the importance of histological ThCFA that appear as IVOCT TCFA, and the false IVOCT appearance of a lipid core under a thick fibrous cap when no histological ThCFA is present—both due primarily to infiltration of foam cells.

We found that the most common mechanisms for the false appearance of IVOCT TCFA and IVOCT ThCFA were punctate or clustered foam cells. Although previous reports suggest that superficial foam cell infiltration may cause the appearance of TCFA,\(^7,\,8\) the high frequency with which this occurs is an important finding of this study and confirms the findings of Fujii et al.\(^\text{10}\) Because atherosclerosis is an inflammatory disease, the high prevalence of foamy macrophages in our samples was expected. Foam cells can cause the appearance of false TCFA and IVOCT ThCFA by...
false TCFA by either type 1 or 2 mechanisms (Figure 1). If the foam cells are punctate in the fibrous cap, they will introduce a large IR gradient and thus type 1 light scattering. If foam cells are concentrated and homogenously distributed, they can appear as a lipid pool with type 2 light scattering. In addition, foam cell infiltration can cause a plaque to appear as a ThCFA when no lipid or necrotic core is present, as identified in 5 of 9 examples (n=4 from punctate foam cells and n=1 from clustered foam cells).

Many true histological TCFA were missed by IVOCT with the requirement that >1 quadrant contain lipid (n=4). Furthermore, no consensus has been met about how many quadrants of an IVOCT image (or the lipid arc) should be dark to be considered a TCFA. Our results argue against an IVOCT requirement of >1 quadrant to define a TCFA. Of 12 true TCFAs, 8 had lipid cores that extended >1 quadrant by IVOCT, 10 had lipid cores that extended >1 quadrant by histology, and 7 had lipid cores that extended >1 quadrant by both IVOCT and histology. In fact, our sensitivity increased from 63% to 87% by categorizing all lipid arcs as TCFA instead of only including obtuse lipid arcs. Further validation of the number of IVOCT defined quadrants or lipid pool arc should be investigated to determine a more accurate definition of IVOCT identified TCFA. Arc measurements taken with IVOCT images may...
studies are needed to resolve these apparent discrepancies.

The discrepancy between IVOCT and histological TCFA studies could be because of the high false-positive rate of IVOCT as demonstrated in this study. Additional imaging systems are needed that can improve the limited PPV identified in the current study. One possibility is to couple a second imaging modality with IVOCT—for instance, intravascular ultrasound, fluorescence lifetime imaging microscopy, near-infrared fluorescence, spectral OCT, or 2-photon luminescence. Two-photon luminescence is an interesting candidate having the ability to image the actual molecular composition of plaque without the use of exogenous contrast agents. For instance, 2-photon luminescence confirmation of the absence of lipid in our TCFA database could have increased PPV to 55% (data not shown). Thus, these multimodal imaging systems all have the advantage of higher PPV over IVOCT alone and may be able to better differentiate between true and false TCFA by specifically identifying the presence or absence of lipid pools.

### Limitations

The results from this small subset of hearts should be validated by a larger study to confirm and expand on the mechanisms of light dropout that appear as TCFAs. Histological coregistration is inherently difficult with imaging studies, and the histological sections are 5-μm thick compared with the 267-μm pitch in IVOCT images. However, the fine serial sectioning of every 120 μm used in the current study greatly improved the accuracy of coregistration. Also, distortions caused by histological processing are always possible sources of error in coregistration and IVOCT image interpretation. Finally, the imaging system we used was from Volcano Corporation, which is not currently clinically available. The optics in the Volcano system are similar to current clinically available systems, however, and thus the results will be applicable to other IVOCT imaging platforms.

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Disclosures
None.

References


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Supplemental Figure. *Summary of current studies that report numbers of TCFAs.* Average numbers of TCFAs reported from 14 studies were calculated.