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Translating Intravascular Optical Coherence Tomography from a Research to a Clinical Tool

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Abstract Intravascular optical coherence tomography (IVOCT) continues to be a hot topic as a method for studying vulnerable plaque in research laboratories across the globe. It is also growing in popularity as a tool for interventional cardiologists to guide percutaneous coronary intervention (PCI). The power of IVOCT for diagnosis of thin-capped fibroatheromas (TCFAs) has yet to receive mainstream clinical attention due to the fact that clinicians still do not have a protocol to follow if TCFA are identified and that TCFA identification requires extensive training in IVOCT image analysis—it is not yet an automated process. In this review, we will discuss the progress of translation of IVOCT from predominantly a research tool to clinical practice by reviewing recent advances in the field of IVOCT for guiding PCI and how the challenge of automated plaque characterization for vulnerable plaque identification is being approached.

Keywords Intravascular optical coherence tomography · Atherosclerosis · Vulnerable plaque · Clinical translation · Spontaneous coronary artery dissection · Plaque erosion · Stent optimization · Quantitation · Automation

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Introduction

Intravascular optical coherence tomography (IVOCT) is an important research tool when used to perform high resolution imaging of the coronary arteries in patients in conjunction with cardiovascular intervention. Application of IVOCT has enabled many advances in our knowledge including (a) time course of biodegradable stent degradation; (b) identification of TCFA in vivo; (c) confirmation of TCFA rupture, plaque erosion, and calcified nodules as primary mechanisms for acute coronary syndromes in patients; (d) differentiation of red and white thrombus; (e) data indicating the time evolution of coverage of bare metal and drug eluting stents; (f) validation of neoatherosclerosis as a mechanism for late stent failure; (g) identification of vessel retraction as a toxicity response to drug eluting stents; and (h) characterization of stent malapposition when stenting acute coronary syndromes due to abluminal clot reabsorption, with many additional insights likely to come. Despite these important mechanistic insights, most cardiologists continue to view IVOCT as a research tool and do not regularly employ this imaging modality to guide their clinical decision-making. The purpose of this article is to review the current literature in five areas relevant to clinical decision-making with the aim of broadening the adoption of IVOCT in cardiology. The five areas examined include use of IVOCT to optimize coronary stent placement; use of IVOCT to properly size biodegradable stents prior to deployment; the use of IVOCT during STEMI to reduce the use of metal stents in cases of plaque erosion and calcified nodules; the proper diagnosis of spontaneous coronary artery dissection; and the use of real-time computer analysis to aid in IVOCT image interpretation of complex coronary atherosclerosis.

Use of IVOCT During Acute Coronary Syndromes (ACS) to Minimize Stent Use in Plaque Erosion and Calcified Nodules

Studies from the Massachusetts General Hospital (MGH) IVOCT registry have demonstrated that in 126 patients, TCFA rupture, plaque erosion, and calcified nodules can be identified in vivo as the cause of ACS in similar frequencies as these etiologies are identified in autopsy studies [1••]. The percentage of IVOCT identified TCFA rupture was 43.7 %, similar to the combined frequency of plaque erosion (31.0 %) and calcified nodules (7.9 %). Further, the MGH IVOCT registry demonstrated that sites of plaque erosion, following removal of the thrombus, have larger lumen diameters and lower stenosis severity compared to TCFA rupture sites. Based on these findings, one may anticipate that those patients with plaque erosion might be able to pursue a strategy of aggressive anticoagulation and clot removal, avoiding stent placement. A stent-free approach is appealing since stent placement in these ACS patients is associated with higher rates of stent thrombosis and plaque/thrombus embolization. The hypothesis is being tested that the stent-free approach is a clinically prudent strategy when plaque erosion is identified with less than 70 % residual stenosis following aggressive treatment of intraluminal thrombus. One study found that in cases of plaque erosion, as identified by IVOCT [1••], patients fared just as well without stents as with stents [2••]. Thirty-one patients with ST-segment elevation myocardial infarction and culprit lesions with plaque erosion (fibrous caps intact) were included in the study. Forty percent of the patients were treated with antiplatelet therapy only, the other 60 % underwent stent placement based on the decision of the cardiologist. At a median follow-up of 753 days, all patients were asymptomatic regardless of whether they had stents placed.

A second study was performed to determine if stenting is always necessary in patients with a large thrombus burden (LTB) [3••]. Specifically, patients with LTB were chosen for this study due to the increased risk of adverse outcomes related to stent malapposition, distal embolization, and late stent thrombosis in these lesions. Patients with LTB (N=101, as assessed by angiography) were included in the study, and 38 % of patients were treated successfully without receiving a stent. IVOCT was performed during the initial percutaneous coronary intervention (PCI) and during a follow-up procedure (0–2, 3–6, or 7–30 days, depending on the preference of the cardiologist). These acute or delayed IVOCT images aided in the decision of whether the avoidance of stent placement was possible due to the presence of plaque erosion at the culprit site without residual stenosis. Authors of the study were able to conclude that patients who did not receive stents had as beneficial outcomes at 1 year as those who did receive stents. This study by Souteyrand et al. demonstrated that IVOCT can be used to help cardiologists decide when stents are necessary and when aggressive anticoagulation and clot removal can be used alone to treat LTB.

These two studies demonstrate that IVOCT can be a useful tool when determining whether stents are a truly necessary part of the therapeutic protocol, which can allow for improved patient care. The extension of these studies to patients with ACS due to calcified nodules is anticipated. Larger studies will be necessary before any changes can be made to current guidelines about non-PCI treatment for cases of plaque erosion.

Use of IVOCT to Size Vessel Lumens for Biodegradable Stent Placement

IVOCT may be applied to accurately measure vessel lumen diameter. IVOCT was applied to measure lumen diameter of phantom vessels and provided higher accuracy in comparison to IVUS, which overestimates, and angiography, which underestimates lumen diameter [4]. Measurement of vessel lumen diameter is particularly important when selecting the size of biodegradable stent to deploy at a target site. While the ductile properties of metallic stents make them forgiving to interventionalists who misjudge final stent diameter by up to 1 mm, the plastic biodegradable stents are more prone to fracture if expanded 0.5 mm beyond the recommended diameter. Thus, greater precision for biodegradable stent sizing is required. Good practice recommends that either IVOCT, IVUS, or quantitative coronary angiography be used to properly size the vessel lumen before selecting the biodegradable stent size [5]. Since IVOCT provides the most accurate measurement of vessel lumen diameter, IVOCT is the preferred imaging modality when deploying biodegradable stents.

IVOCT to Guide Stent Deployment and Improve Patient Outcomes

Stenting of coronary arteries is performed during PCI to improve patient symptoms. However, stenting can also be associated with complications (e.g., stent thrombosis and restenosis). Use of IVUS to optimize stent placement has been demonstrated to reduce mortality, infarction, restenosis, and stent thrombosis [6]. One may expect that imaging with IVOCT to guide stent deployment would similarly improve patient outcomes. Although prospective studies with IVOCT have not been performed to date, a large retrospective study (CLI-OPCI) demonstrates that IVOCT imaging improves patient outcomes when used in conjunction with stent placement [7••]. In this retrospective trial of 670 patients, 335 patients undergoing PCI with angiography and IVOCT were matched to 335 patients undergoing angiography alone. In the former group, the interventionalist was allowed to view the OCT image and was given instructions on how to make additional treatment decisions based on IVOCT findings. These findings included stent struts more than 200 μm off the vessel wall where larger balloons were allowed,

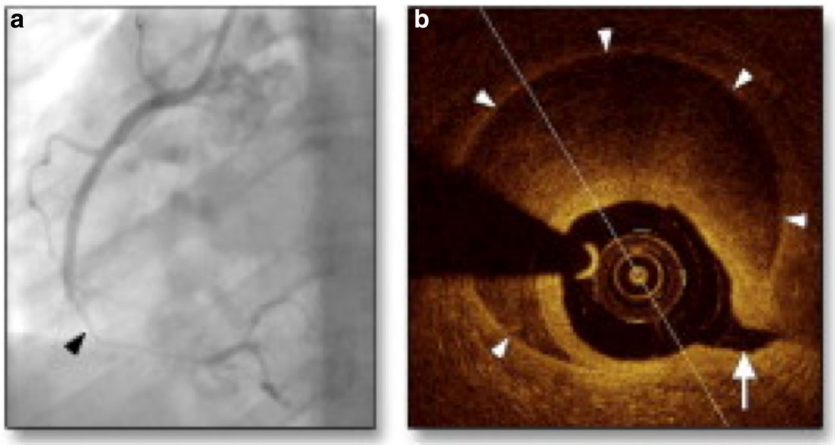

Fig. 1 Spontaneous coronary artery dissection (SCAD). **a** Angiogram of right coronary artery shows some stenosis at the *arrowhead*. **b** The IVOCT image from the *arrowhead* in **a** reveals the source of stenosis to be an intramural hematoma caused by SCAD. The *white arrow* points to a side branch [25]. Reprinted from JACC: Cardiovascular Imaging, 5/10, TW Johnson, D Smith, JW Strange, et al., Spontaneous Multivessel Coronary Intramural Hematoma An Insight With OCT, 1070–1, Copyright (2012), with permission from Elsevier

and stent edge dissections more than 200 μm off the vessel wall and reference lumen area less than 4 mm^2, both where an additional stent should be placed, among others. In one third of the IVOCT group, additional interventions were performed based on the IVOCT imaging information. At 12 month follow-up, the IVOCT group had significantly lower risk of cardiac death (1.2 vs 4.5 %, P=0.010), cardiac death or MI (6.6 vs 13.0 %, P=0.006), and composite of cardiac death, MI, or repeat revascularization (9.6 vs 14.8 %, P=0.044) [7••]. Thus, the study concluded that IVOCT guidance of PCI is not only safe but also improves patient outcomes. A randomized prospective trial is planned to confirm these findings in the future (Illumium 4).

IVOCT Advances in the Diagnosis of Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection (SCAD) causes separation of the coronary wall (either at intima-media or media-adventitia interface) and the creation of a false lumen, which may extend into the arterial wall as an intramural hematoma. SCAD can result in myocardial infarction, ventricular arrhythmias, and sudden cardiac death and disproportionately affects young women (particularly those with fibromuscular dysplasia). SCAD can be difficult to visualize with angiography and thus is a commonly missed cause of acute coronary syndromes (ACS) but can be diagnosed with intracoronary imaging including IVUS and IVOCT [8••]. For instance, two studies focused on women under 50 years old with ACS found that only 8.7 % were found to have SCAD when diagnosed with angiography alone [9], but 24 % were found to have SCAD when IVOCT was utilized [10•]. This demonstrates that SCAD is a more common cause of ACS in younger women than angiography alone would suggest and that IVOCT is an important diagnostic tool for this condition. Besides the easily recognized separation of the arterial wall with intracoronary imaging, more subtle is the classic IVOCT image of circumferential intramural hematomas, where packing of red blood cells of identical index of

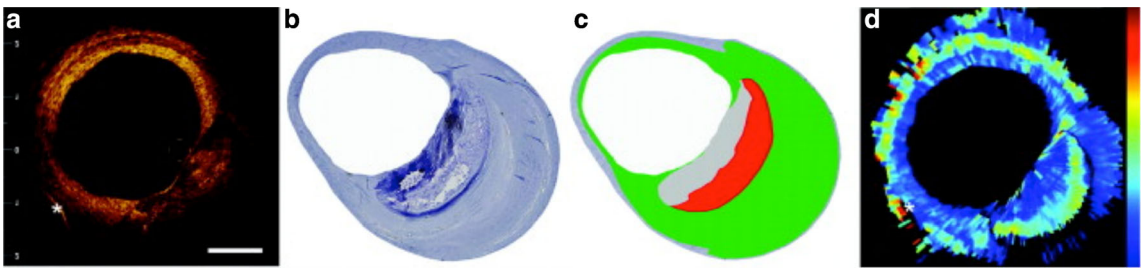

Fig. 2 IVOCT attenuation imaging. **a** OCT image of a coronary atherosclerotic lesion ex vivo: *Asterisk* indicates the needle used for marking the imaged site; the length of the white scale bar is 1 mm; **b** corresponding histology, H&E stain; **c** cartoon histology, overlayed on the original histology slide, indicating an advanced necrotic core (*red*) behind a calcification (*gray*), and a slight fibrotic (*green*) circumferential intimal thickening; and **d** IVOCT-derived attenuation coefficient μ_t, plotted on a continuous linear color scale from 0 to 15 mm^{-1}. The area corresponding to the necrotic core exhibits a higher attenuation coefficient (8 to 10 mm^{-1}) than the calcification next to it or the surrounding fibrous tissue (2 to 3 mm^{-1}) [12]. Reprinted with permission from van Soest G, Goderie T, Regar E, et al.: Atherosclerotic tissue characterization in vivo by optical coherence tomography attenuation imaging. Journal of biomedical optics (2010) 15(1):011105

refraction (IR) results in light transmission and identification of the external elastic lamina (Fig. 1).

The Use of Real-Time Computer Analysis to Aid in IVOCT Image Interpretation of Coronary Atherosclerosis

Although IVOCT can record images of plaque that contain features that suggest vulnerability, the interpretation of these images currently requires extensive training. Further, due to the lack of automated image analysis, investigators and/or cardiologists interpret IVOCT images subjectively. As a result, identification of vulnerable plaque with IVOCT is still predominantly performed in research laboratories. To automate identification of vulnerable plaque with IVOCT, two steps are required: (1) quantification of the IVOCT image specific to each anatomic feature (e.g., fibrous cap and lipid pool) and (2) automated interpretation of the quantified IVOCT image.

Attenuation and Backscattering Coefficients for Segmentation

Some work has been performed using attenuation and scattering coefficients measured from the IVOCT signal to aid in the identification of plaque components. Xu et al. performed a

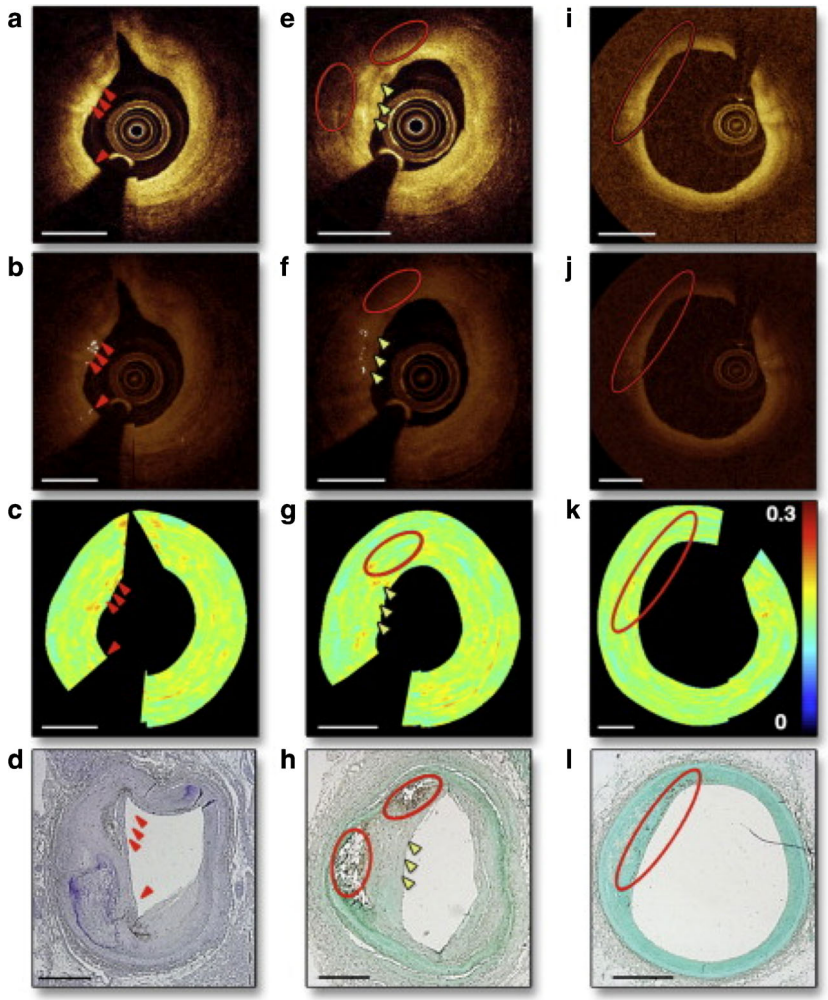

Fig. 3 Macrophages depicted by the quantitative bright spot detection method. **a** Unprocessed intravascular optical coherence tomography (IVOCT) image with visible bright spots (*red arrows*). **b** Algorithm-processed IVOCT image with bright spots identified. **c** Normalized SD (NSD) image. **d** CD68 stain showing that bright spots were caused by macrophages. **e** Unprocessed IVOCT image with bright spots (*yellow arrows*) and shadows (*red circles*) caused by macrophages. **f** Algorithm processed IVOCT image with bright spots identified. **g** NSD image. **h** CD68 stain showing that bright spots came from a region of macrophage positivity and that the red circled macrophage pool was depicted as a shadow in **e** and **f.** **i** Unprocessed IVOCT image from a region with macrophages far from the catheter. **j** Algorithm-processed IVOCT image showing that bright spots were not found in the CD68þ region. **k** NSD image. **l** CD68 stains showing macrophage positivity in the *red circle*. This region was too far from the catheter for the signal to identify bright spots. All *scale bars* are 1 mm [18••]. Reprinted from *JACC Cardiovasc Imaging*, 8/1, Phipps JE, Vela D, Hoyt T, et al., Macrophages and intravascular oct bright spots: A quantitative study, 63–72, Copyright (2014), with permission from Elsevier

study on coronary artery cross sections that measured backscattering and attenuation coefficients. This study was very precise because it performed IVOCT on thin histology cross sections of tissue. Thus, the IVOCT signal that the coefficients were estimated from was accurately co-registered with the histology of pure plaque components, not mixtures of multiple types. Backscattering coefficients were reported for fibrous tissue (18.6±6.4 mm^{-1}), lipid (28.1±8.9 mm^{-1}), and calcium (4.9 ±1.5 mm^{-1}). Attenuation coefficients were also reported for fibrous tissue (6.4±1.2 mm^{-1}), lipid (13.7±4.5 mm^{-1}), and calcium (5.7±1.4 mm^{-1}) [11]. This method needs further validation and development before clinical implementation will be feasible.

More recently, attenuation coefficients were computed from the IVOCT signal and were implemented in vivo (Fig. 2) [12]. The authors identified attenuation coefficients as follows: healthy vessel and intimal thickening (2–5 mm^{-1}), healthy vessel wall enveloped by a circumferential high-attenuation layer (>12 mm^{-1}), necrotic core (>10 mm^{-1}), and macrophage infiltration (>12 mm^{-1}) [12]. Their samples did not include calcium, so these results cannot be compared with the previous conflicting attenuation coefficients of calcium [11], but as observed by Xu et al., lipidic plaque demonstrates a higher attenuation coefficient compared to fibrous tissue. This past year, IVOCT attenuation imaging was used to quantify the vascular healing response 5 years after everolimus-eluting bioresorbable vascular scaffolds were implanted in 14 patients. In this study, maximum attenuation coefficients were found to very closely correspond to locations that an expert IVOCT reader identified as necrotic cores. This result is consistent with the previous studies that found necrotic cores to have the highest attenuation coefficients and further demonstrates the potential value of attenuation coefficients for IVOCT vulnerable plaque imaging [13].

Macrophage Identification

Aside from characterization of the major plaque tissue types (lipidic, fibrous, fibrocalcific), investigators continue to investigate whether IVOCT can be used to identify smaller features associated with plaque vulnerability such as macrophages [14]. The first paper to describe OCT quantification of macrophages was published in 2003 by Tearney et al. [15]. Cadaver aortas and carotid bulbs were imaged *en face* with OCT and then stained with H&E, Masson's trichrome, CD68, and α-actin monoclonal antibody (for smooth muscle cells). Normalized standard deviation (NSD) in 500×125 μm (lateral× axial) regions in the fibrous cap were calculated. NSD values were compared with macrophage and smooth muscle cell presence by correlating with percentage of positive staining in the CD68 and α-actin immunohistochemistry analyses, respectively. A positive linear correlation was found between raw OCT NSD and %CD68 staining (R=0.84). Smooth muscle cells were not found to be the cause of the increased NSD values. Bright spots in OCT images cause an increase in NSD due to differences in the optical IR of plaque components.

The first clinical implementation of the Tearney et al. method for macrophage imaging was published by MacNeill et al. in 2004 [16]. Patients undergoing percutaneous coronary interventions for stable angina pectoris, unstable angina pectoris, and ST-segment elevation myocardial infarction were evaluated with IVOCT. The density of bright spots observed in IVOCT images increased in unstable patients. However, the density of bright spots did not vary between culprit and remote lesions in the same vessel within individual patients, suggesting a limitation of this method. Bright spot density was observed to be significantly higher at sites of plaque rupture compared to non-ruptured sites [16].

More recently, some investigators have raised the question whether bright spots in IVOCT images are caused only by macrophages [17]. A study was performed that assessed histologic sources of bright spots in IVOCT images and found that these features may result from any plaque components

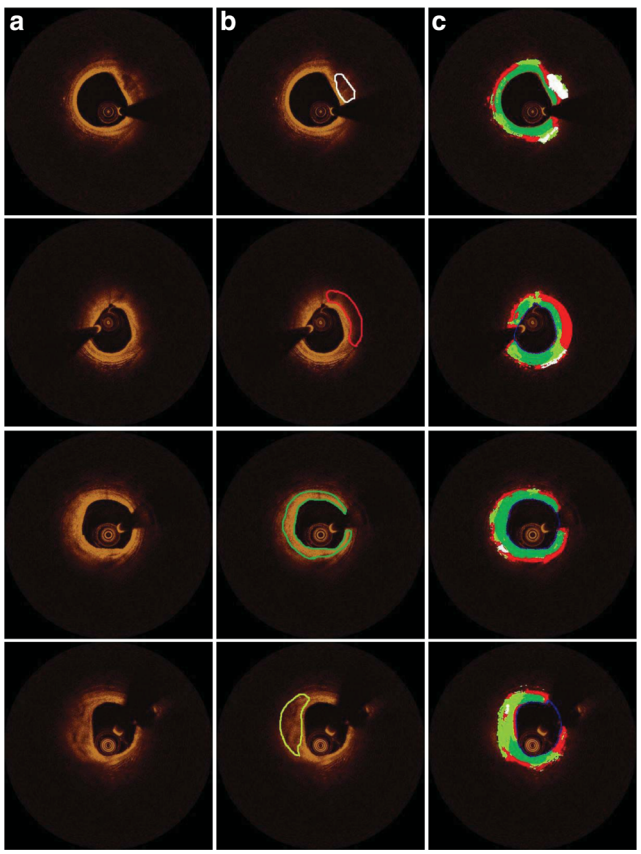

Fig. 4 Examples of the automated classification method by Athanasiou et al. **a** Initial images, **b** annotations over the initial images (*white-calcium*, *red-lipid*, *green-fibrous*, and *light green mixed plaque*) over the initial image, **c** color-coded images produced by our methodology using the initial images [20•]. Reprinted with permission from Athanasiou LS, Bourantas CV, Rigas G, et al.: Methodology for fully automated segmentation and plaque characterization in intracoronary optical coherence tomography images. J Biomed Opt (2014) 19(2):026009

that introduce a change in IR in the tissue (including lipid-rich macrophages (foam cells) in fibrous tissue (Fig. 3)) [18••]. A quantitative algorithm was developed to identify the bright spots while accounting for the distance from the catheter, depth in the tissue, and signal-to-noise ratio. A detailed histologic analysis revealed that the changes in IR in the coronary arteries of the 10 ex vivo hearts imaged in this study could be caused by a number of etiologies, e.g., cholesterol clefts in necrotic cores, cellular or hypocellular fibrous tissue, areas of plaque layering or interface such as the interface of old and new fibrous tissue, the intimal/medial or adventitial/medial interface, calcium/fibrous interface, fibrous cap/lipid pool interface and neovascularization/media interface, as well as all of these etiologies in the presence of foam cells (Fig. 3). Additionally, it was found that pools of macrophages were commonly associated with dark regions in IVOCT images and not necessarily bright spots [18••].

Based on studies using two available quantification techniques for bright spot identification, the method by Phipps et al. demonstrates that although macrophages can cause bright spots, they are not the only etiology that is associated with bright spots. Thus, observation of bright spots in IVOCT images of coronary arteries should be interpreted with some degree of caution.

Automation of Vulnerable Plaque Detection

Automation of plaque characterization with IVOCT will be required for accurate vulnerable plaque detection—just as virtual histology revolutionized plaque characterization for IVUS. The current qualitative IVOCT image analysis methods employed require extensive human interaction and result in variability in interpretations between investigators. Automation of IVOCT vulnerable plaque detection would represent a significant advancement for this imaging technology.

A semi-automatic calcium detection method has been demonstrated [19]. The method required minimal user input and had a 78±9 % accuracy in identification of calcified plaque in comparison to expert manual identification in 106 images from eight patients [19].

Another study implemented a Random Forests classifier to automate plaque classification into four types: calcium, lipid pool, fibrous tissue, and mixed plaque (Fig. 4) [20•]. Using intensity and texture-based features derived from 27 IVOCT pullbacks (22 patients), the classification algorithm compared to an expert IVOCT reader identified the lumen, calcium, lipid, fibrous tissue, and mixed plaque with a Pearson's correlation coefficient of 0.99, 0.96, 0.96, 0.97, and 0.96, respectively, and positive predictive value 0.98, 0.83, 0.76, 0.78, and 0.74, respectively [20•]. The limitations of this study were a lack of comparison with histology and a lack of further characterizing the "mixed plaque" group into more specific plaque components.

The Random Forests classification method was also implemented by Ughi et al. for plaque characterization in human arteries [21•] and classification of neointimal stent coverage in a rabbit model [22•, 23•]. The method of calculating statistical texture parameters was used to quantify the IVOCT signal in all three of these studies; in addition, backscattering and attenuation coefficients were used in the human artery study. For human arteries, 49 in vivo data sets were used to train the

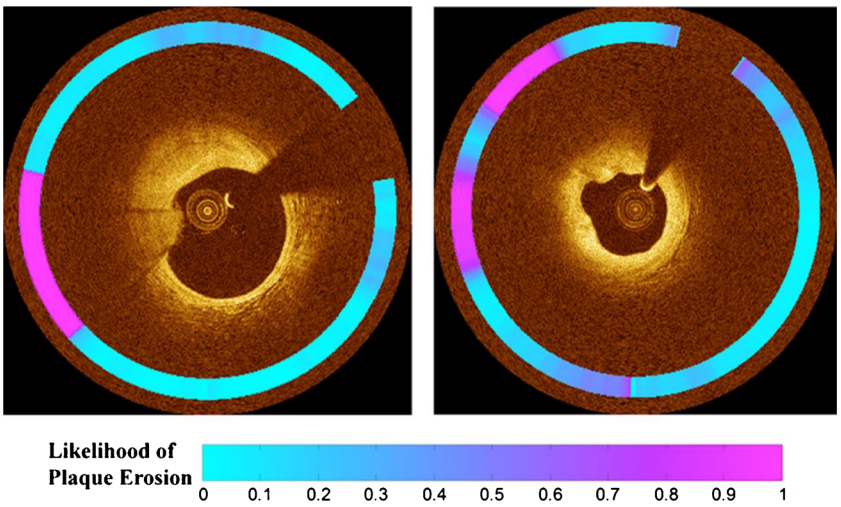

Fig. 5 Automated labeling of plaque erosion. Two examples of optical coherence tomographic images are labeled automatically for the likelihood of plaque erosion. At each angular position, the region of interest (ROI) was selected automatically as a 10° region bounded radially by the lumen boundary and the vessel wall. The algorithm was then applied to the ROI, and the likelihood of plaque erosion can be generated for this position. The entire vessel can therefore be automatically labeled in a continuous colormap indicating the likelihood of plaque erosion [24•]. Reprinted with permission from Wang Z, Jia H, Tian J, Soeda T, Vergallo R, Minami Y, Lee H, Aguirre A, Fujimoto JG, Jang IK: Computer-aided image analysis algorithm to enhance in vivo diagnosis of plaque erosion by intravascular optical coherence tomography. Circ Cardiovasc Imaging (2014) 7(5):805–810

classification algorithm and validation was performed based on manual assessment of 64 plaques from the dataset. An overall accuracy of 81.5 % was found with per class accuracies of 89.5, 72.1, and 79.5 % for fibrotic, calcified, and lipid-rich plaques, respectively. The attenuation and backscattering coefficients measured were in agreement with previous studies by Xu et al. [11] and van Soest et al. [12]. This study also was limited by a lack of comparison to histology. The Random Forests classification method using texture analysis as a quantification method was then applied to automate the distinction between mature and immature stent coverage in an atherosclerotic New Zealand white rabbit model. Mature tissue has a high intensity, smooth and homogenous IVOCT signal compared to immature tissue, which has low intensity. Using a pixel-wise classification method on 53 IVOCT images paired with histology, accuracy was 87 %; but when regions were selected by hand for 72 regions of interest from 33 IVOCT images, accuracy increased to 92 % with a sensitivity and specificity of 91 and 93 %, respectively [22•]. The method for this study was then extrapolated to compare human, qualitative analysis of stent coverage to the automated method [23•]. The authors found excellent agreement between automated and manual analysis (R= 0.95, P<0.001), between automated analysis and histology (R=0.85, P<0.001), and between manual analysis and histology (R=0.83, P<0.001). These results suggest an automated method is feasible and a reasonable approach for clinical implementation.

An automated method of enhancing in vivo diagnosis of plaque erosion has recently been reported [24•]. A computer algorithm was developed that uses optical (mean intensity at surface of tissue, mean intensity of region of interest, attenuation coefficient, and normalized standard deviation) and morphological properties (tissue protrusion area and roughness of tissue surface) of the tissue in a logistic regression classification algorithm to identify the likelihood that a region of an IVOCT image contains plaque erosion (Fig. 5) [24•]. With a 10-fold cross validation, the accuracy of the algorithm was 97.6 % for identifying plaque erosion in 42 patients. This is the first work to quantify and automate the identification of erosion in IVOCT images for in vivo analysis.

Attenuation and backscattering coefficients have been validated with histology (though complete agreement among investigators is lacking), and NSD and bright spot analysis have been validated with histology as well. Additionally, comparing mature and immature stent tissue was validated in a rabbit model with histology. However, texture analysis statistics, the Random Forests classification method, and the plaque erosion detection method have not been compared to histology in humans, which should be completed before methods for automated vulnerable plaque classification can be implemented clinically.

Conclusion

We have demonstrated four areas where IVOCT can positively affect diagnosis (plaque erosion and SCAD) and therapy (optimizing stenting results and proper sizing of biodegradable stents) for patients with coronary pathology. The identification of vulnerable plaque by IVOCT is not as mature due to the complexity of the images—but investigators are currently using computer automation to simplify this analysis. While important advances have been made in image quantification and automation, these algorithms still need to undergo more rigorous studies with histologic validation and, ultimately, prospective clinical trials before they can also be implemented clinically. While the bias of most clinicians is that IVOCT remains a research tool, there are many areas where IVOCT can now impact clinical decision-making and therapy. With further education and training of interventional cardiologists, we anticipate that the technology may become more broadly utilized.

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Compliance with Ethics Guidelines

Conflict of Interest JE Phipps, T Hoyt, TE Milner, MD Feldman all declare no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol. 2013;62(19):1748–58. **IVOCT is demonstrated to diagnose both types of vulnerable plaque: erosion and calcified nodule, in addition to the already known ability of IVOCT to diagnose TCFA**.

2.•• Prati F, Uemura S, Souteyrand G, Virmani R, Motreff P, Di Vito L, et al. Oct-based diagnosis and management of stemi associated with intact fibrous cap. JACC Cardiovasc Imaging. 2013;6(3):283–7. **IVOCT is used to demonstrate that when plaques with intact fibrous caps can be treated with antiplatelet therapy and do not need to be stented**.

3.•• Souteyrand G, Amabile N, Combaret N, Hammas S, Prati F, Berry C, et al. Invasive management without stents in selected acute coronary syndrome patients with a large thrombus burden: a prospective study of optical coherence tomography guided treatment decisions. EuroInterv. 2014. **This study shows that IVOCT can be**

used to identify patients with erosion and that these patients do just as well with as without stents.

4. Kubo T, Akasaka T, Shite J, Suzuki T, Uemura S, Yu B, et al. Oct compared with ivus in a coronary lesion assessment: the opus-class study. JACC Cardiovasc Imaging. 2013;6(10):1095–104.
5. Tamburino C, Latib A, van Geuns RJ, Sabate M, Mehilli J, Gori T, et al. Contemporary practice and technical aspects in coronary intervention with bioresorbable scaffolds: a european perspective. Euro Interv. 2015;10(10).
6. Jang JS, Song YJ, Kang W, Jin HY, Seo JS, Yang TH, et al. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. J Am Coll Cardiol Intv. 2014;7(3):233–43.

7.•• Prati F, Di Vito L, Biondi-Zoccai G, Occhipinti M, La Manna A, Tamburino C, et al. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: The centro per la lotta contro l'infarto-optimisation of percutaneous coronary intervention (cli-opci) study. Euro Interv. 2012;8(7):823–9. **When IVOCT is used in conjunction with angiography during PCI, patients will have improved outcomes**.

8.•• Yip A, Saw J. Spontaneous coronary artery dissection-a review. Cardiovasc Diagn Ther. 2015;5(1):37–48. **Discusses the importance of spontaneous coronary artery dissection and how it is optimally diagnosed with IVOCT**.

9. Vanzetto G, Berger-Coz E, Barone-Rochette G, Chavanon O, Bouvaist H, Hacini R, et al. Prevalence, therapeutic management and medium-term prognosis of spontaneous coronary artery dissection: results from a database of 11,605 patients. European J Cardiothorac Surg: Off J Eur Assoc Cardiothorac Surg. 2009;35(2):250–4.

10.• Saw J, Aymong E, Mancini GB, Sedlak T, Starovoytov A, Ricci D. Nonatherosclerotic coronary artery disease in young women. Can J Cardiol. 2014;30(7):814–9. **This article sheds light on the prevalence of SCAD in young women**.

11. Xu C, Schmitt JM, Carlier SG, Virmani R. Characterization of atherosclerosis plaques by measuring both backscattering and attenuation coefficients in optical coherence tomography. J Biomed Opt. 2008;13(3):034003.
12. van Soest G, Goderie T, Regar E, Koljenovic S, van Leenders GL, Gonzalo N, et al. Atherosclerotic tissue characterization in vivo by optical coherence tomography attenuation imaging. J Biomed Opt. 2010;15(1):011105.
13. Karanasos A, Simsek C, Gnanadesigan M, van Ditzhuijzen NS, Freire R, Dijkstra J, et al. Oct assessment of the long-term vascular healing response 5 years after everolimus-eluting bioresorbable vascular scaffold. J Am Coll Cardiol. 2014;64(22):2343–56.
14. Cilingiroglu M, Oh JH, Sugunan B, Kemp NJ, Kim J, Lee S, et al. Detection of vulnerable plaque in a murine model of atherosclerosis with optical coherence tomography. Catheter Cardiovasc Interv Off J Soc Cardiac Angiograph Interv. 2006;67(6):915–23.
15. Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. Circulation. 2003;107(1):113–9.
16. MacNeill BD, Jang IK, Bouma BE, Iftimia N, Takano M, Yabushita H, et al. Focal and multi-focal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. J Am Coll Cardiol. 2004;44(5):972–9.
17. Brezinski ME. Capabilities, limitations, and misconceptions of using oct to assess vulnerable plaques. Nat Rev Cardiol. 2014;11(11):638.

18.•• Phipps JE, Vela D, Hoyt T, Halaney DL, Mancuso JJ, Buja LM, et al. Macrophages and intravascular oct bright spots: a quantitative study. JACC Cardiovasc Imaging. 2014. **Bright spots in IVOCT images are representative of changes in optical index of refraction that can be caused by numerous plaque etiologies, not only macrophages.**

19. Wang Z, Kyono H, Bezerra HG, Wang H, Gargesha M, Alraies C, et al. Semiautomatic segmentation and quantification of calcified plaques in intracoronary optical coherence tomography images. J Biomed Opt. 2010;15(6):061711.

20.• Athanasiou LS, Bourantas CV, Rigas G, Sakellarios AI, Exarchos TP, Siogkas PK, et al. Methodology for fully automated segmentation and plaque characterization in intracoronary optical coherence tomography images. J Biomed Opt. 2014;19(2):026009. **Demonstrates an automated method for both segmenting and characterizing plaque with IVOCT images**.

21.• Ughi GJ, Adriaenssens T, Sinnaeve P, Desmet W, D'Hooge J. Automated tissue characterization of in vivo atherosclerotic plaques by intravascular optical coherence tomography images. Biomed Opt Express. 2013;4(7):1014–30. **Statistical texture analysis parameters combined with attenuation and backscattering coefficients can be combined to automate atherosclerosis characterization into three components: fibrous, lipid and calcium**.

22.• Ughi GJ, Steigerwald K, Adriaenssens T, Desmet W, Guagliumi G, Joner M, et al. Automatic characterization of neointimal tissue by intravascular optical coherence tomography. J Biomed Opt. 2014;19(2):21104. **Mature from immature neointimal tissue can be distinguished using IVOCT in a rabbit model of atherosclerosis**.

23.• Ughi GJ, Van Dyck CJ, Adriaenssens T, Hoymans VY, Sinnaeve P, Timmermans JP, et al. Automatic assessment of stent neointimal coverage by intravascular optical coherence tomography. Eur Heart J Cardiovasc Imaging. 2014;15(2):195–200. **Mature from immature neointimal tissue can be distinguished using IVOCT in the clinical setting**.

24.• Wang Z, Jia H, Tian J, Soeda T, Vergallo R, Minami Y, et al. Computer-aided image analysis algorithm to enhance in vivo diagnosis of plaque erosion by intravascular optical coherence tomography. Circ Cardiovasc Imaging. 2014;7(5):805–10. **Demonstrates for the first time an automated method to enhance diagnosis of plaque erosion in vivo**.

25. Johnson TW, Smith D, Strange JW, Bucciarelli-Ducci C, Lowe R, Baumbach A. Spontaneous multivessel coronary intramural hematoma: an insight with oct. JACC Cardiovasc Imaging. 2012;5(10):1070–1.