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EDITORIAL COMMENT

Synergizing Light and Machine Learning to Comprehensively Reveal Coronary Plaque Composition*

Eric A. Osborn, MD, PhD,[a] Nicholas E. Houstis, MD, PhD,[b] Farouc A. Jaffer, MD, PhD[b]

A single sunbeam is enough to drive away many shadows.
—Francis of Assisi (1182–1226) (1)

Atherosclerosis progression and destabilization underlie the life-threatening complications of coronary artery disease (CAD). Histopathological studies show that high-risk atherosclerotic plaques are associated with certain structural, biochemical, and pathobiological features, including lipid-rich necrotic cores, thinned fibrous caps, infiltrating macrophages with inflammatory protease activity, and dysfunctional endothelium, among others. At present, stand-alone structural imaging of plaque morphology with clinical intravascular ultrasound (IVUS) and optical coherence tomography (OCT) incompletely define high-risk plaques that cause future events. In part, this limitation relates to the complex interplay of plaque structure, biochemistry, and pathobiology, as well as systemic factors of hypocoagulability and inflammation. Recent approaches have addressed this limitation by harnessing multimodality imaging, yielding progress in improving atherosclerosis risk prediction (2). Notable clinical successes include integrated endothelial shear stress-IVUS and integrated near-infrared spectroscopy (NIRS)-IVUS, which are used to examine arterial hemodynamics and plaque lipid, respectively, in concert with IVUS plaque structure. Translatable multimodal technologies incorporating OCT are sparser, and currently include OCT-NIR autofluorescence (NIRAF) to assess oxidative stress and intraplaque hemorrhage, and IVUS-OCT structural-structural imaging. Importantly, although many translatable intracoronary approaches are available to assay plaque features, no single method has yet established clinically routine predictive ability.

Another promising optical imaging approach is fluorescence lifetime imaging (FLIm), a technique that measures the fluorescence decay rate of each component of plaque autofluorescence. After excitation with 355 nm ultraviolet light, FLIm is detected in wavelengths spanning 380 to 560 nm to form an image based on differential fluorescence lifetimes. As with fluorescence imaging, FLIm is not depth resolved (unlike IVUS or OCT), but an advantage of FLIm is that it can isolate multiple biochemical components according to each constituent's unique fluorescence decay lifetime (time constant), even if the components fluoresce at the same wavelength. FLIm has already shown clinical utility in several disciplines, such as for imaging retinal disease. In atherosclerosis, FLIm can resolve lipid, calcium, and fibrous tissue based on unique fluorescence lifetime signatures, as well as plaque macrophages, the principal inflammatory cell underlying plaque progression and destabilization. Furthermore, by examining tissue autofluorescence, FLIm does not rely upon the administration of any exogenous signal-enhancing targeting molecules, distinguishing itself from molecular imaging approaches that require intravenous injection of targeted imaging agents. In terms of clinical translation, IVUS-FLIm performed with a

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From the [a]Cardiology Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; and the [b]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA.

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dual-mode coronary artery catheter revealed excellent plaque component discrimination in human CAD ex vivo (3).

In this issue of *JACC: Basic to Translational Science*, Kim et al (4) investigate multimodal intracoronary OCT-FLIm plaque imaging in a pig coronary atherosclerosis model in vivo. The custom-built OCT-FLIm system is packaged in a coronary-compatible 2.9F catheter, enhancing translatability. In pigs with hyperlipidemia and streptozotocin-induced diabetes, and then subjected to local coronary balloon injury to spur atherosclerosis, the investigators performed intracoronary OCT-FLIm to simultaneously detect various coronary plaque components including lipids, macrophages, and fibrous tissue. OCT-FLIm was safe and highly reproducible (intraclass correlation coefficient >0.9 using repeated imaging pullbacks). On detailed comparative analysis with histopathology (performed both per 1° circumference arc and per cross-sectional frame average), the investigators found improved OCT-FLIm plaque characterization compared to standalone OCT. FLIm also improved macrophage identification, uncovering additional macrophage-rich zones not apparent by OCT. Notably, due to limited tissue light penetration (~200 μm), FLIm is a surface-weighted imaging modality that characterizes superficial plaque components while deeper plaque structures are unable to be interrogated. Fortunately, many high-risk plaque features reside close to the lumen-blood interface, including thin cap fibroatheroma, thrombus, superficial macrophages, and calcium nodules, all within the sensing depth of FLIm. Overall, the current work establishes OCT-FLIm as a new, translatable hybrid imaging approach for coronary plaque characterization in vivo. Compared to IVUS-FLIm, advantages of OCT-FLIm include high-speed data acquisition (up to 40 mm/s pullback) through a blood-free environment required for both OCT and FLIm assessment (flushing and high-speed pullbacks are not clinically standard IVUS practice at present).

A major limitation of clinical intracoronary imaging (and cardiovascular imaging in general) is the tension that arises between the substantial volume of data generated per imaging study and the need to provide real-time decisions at the point-of-care. Manual plaque characterization from intracoronary imaging data can take hours to complete, but decision-making in the cardiac catheterization laboratory may need to be performed within minutes of image acquisition — for example, to enable optimal percutaneous treatment of culprit and nonculprit plaques. In addition to the volume of data, as the complexity of multimodal image data spirals, manual analysis becomes increasingly untenable. In the current study, the investigators furthered the translatability of OCT-FLIm by leveraging machine learning techniques to automate plaque analysis. Using histopathology of pig coronary atherosclerosis as ground truth, they succeeded in training a random forest classifier to discriminate among 5 biochemical components of atherosclerosis. In this proof-of-concept study, the classifier performed well with a classification accuracy of 94% in cross-validation. Moreover, on modern computing hardware computational times for plaque classification would be expected to satisfy the constraints of point-of-care analysis. However, applying this approach to humans will require retraining the classifier on a meticulously assembled ground truth data set of human coronary plaque. For the classifier to generalize well, this data set will need to capture variation from all sources, from the spectrum of human plaques (as discussed below) to contextual factors such as the impact of neighboring structures on autofluorescence (eg, in thin-walled arteries). Such a data set, together with modern machine learning algorithms, should enable OCT-FLIm to realize its potential of providing plaque composition analysis in real-time.

While the current work by Kim et al (4) represents an important step for intracoronary OCT-FLIm translation, there are several areas to be addressed as this technology moves toward patient care. One important distinction is that pig atherosclerosis, although an accepted preclinical model, generates early-stage lesions that do not recapitulate features of advanced CAD, such as bulk- and microcalcifications, necrotic cores, intraplaque hemorrhage, and plaque erosion. Thus, to guide OCT-FLIm forward, further validation and performance assessment of automated OCT-FLIm plaque characterization in human plaques are needed. In particular, the impact of calcium, which is not observed in short-term pig atherosclerosis models, will need to be comprehensively assessed by OCT-FLIm in human CAD. However, given the published agreement between IVUS-FLIm and histology in human coronary atheroma (3), there is similar potential for OCT-FLIm. Should OCT-FLIm become clinically available, studies will need to establish whether OCT-FLIm comprehensive plaque composition can provide additive value beyond standalone OCT and NIRS-IVUS (both capable of structure and lipid detection) to improve risk prediction.

Intracoronary OCT-FLIm thus joins a growing set of hybrid imaging approaches that aim to provide complementary information related to coronary plaque structure and/or pathobiology. Such multimodal

approaches may one day converge to unlock the secrets of high-risks plaques that cause adverse events. In the future, development of a trimodality IVUS-OCT-FLIm catheter might allow greater plaque characterization by adding IVUS assessment of plaque burden, a key predictor identified in the PROSPECT (An Imaging Study in Patients With Unstable Atherosclerotic Lesions) atherosclerosis natural history study. Nonetheless, with the capability for robust and rapid multicomponent plaque assessment, OCT-FLIm imaging has the potential to uncover important new pathophysiological insights, such as whether FLIm-detected macrophages are linked to plaque progression in patients. In the meantime, parallel paths are being pursued with different emerging biological imaging modalities, such as near-infrared fluorescence (NIRF) molecular imaging (paired with IVUS or OCT) to detect cathepsin protease inflammatory activity as a harbinger of plaque growth (5). Clinical OCT-NIRAF imaging has also been safely tested in the human coronary environment (6). In the coming years, with the continued expansion of available technologies, it will be exciting to watch the next chapter of hybrid intracoronary imaging systems unfold, as they all compete to resolve important translational issues related to high-risk plaque identification and treatment strategies. Using rapid and reliable machine learning algorithms to analyze large data sets and present the salient findings in a meaningful way to the treating physician will be instrumental in this process. We look forward to the clinical translation of OCT-FLIm, and the growth of multimodal intracoronary imaging in general, to provide comprehensive atherosclerosis assessment, recognizing that in imaging, as in life, the whole is often greater than the sum of its parts.

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ADDRESS FOR CORRESPONDENCE: Dr Farouc A. Jaffer, Massachusetts General Hospital-Cardiovascular Research Center, Simches Research Building, 55 Fruit Street, Room 3206, Boston, Massachusetts 02114, USA. E-mail: fjaffer@mgh.harvard.edu.

REFERENCES

1. BrainyQuotes. Francis of Assisi quotes. Accessed October 29, 2021. https://www.brainyquote.com/quotes/francis_of_assisi_753007

2. Bourantas CV, Jaffer FA, Gijsen FJ, et al. Hybrid intravascular imaging: recent advances, technical considerations, and current applications in the study of plaque pathophysiology. *Eur Heart J*. 2017;38:400–412.

3. Bec J, Vela D, Phipps JE, et al. Label-free visualization and quantification of biochemical markers of atherosclerotic plaque progression using intravascular fluorescence lifetime. *J Am Coll Cardiol Img*. 2021;14:1832–1842.

4. Kim S, Nam HS, Lee MW, et al. Comprehensive assessment of high-risk plaques by dual-modal imaging catheter in coronary artery. *J Am Coll Cardiol Basic Trans Science*. 2021;6:948–960.

5. Osborn EA, Ughi GJ, Verjans JW, et al. Intravascular molecular-structural assessment of arterial inflammation in preclinical atherosclerosis progression. *J Am Coll Cardiol Img*. 2021;14:2265–2267.

6. Ughi GJ, Wang H, Gerbaud E, et al. Clinical characterization of coronary atherosclerosis with dual-modality OCT and near-infrared autofluorescence imaging. *J Am Coll Cardiol Img*. 2016;9:1304–1314.

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