EDITORIAL COMMENT

Will Intravascular OCT Shed Light on Vascular Biology?*

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The regulatory imperatives of contemporary medicine require extensive pre-clinical and clinical investigations to properly evaluate the risks and benefits of novel therapies. Yet, it was only after hundreds of thousands of devices had been implanted in humans that we “discovered” the inadequate vascular healing associated with deployed drug-eluting stents (DES) (1). The reason for our delay in understanding the vascular response to DES is multifactorial, but certainly in part centers on the limitations of the available tools to assess mechanisms of rare events. Current in vivo imaging technologies are inadequate to assess DES, and investigators have had to rely on limited ex vivo data (1,2). Furthermore, differences in the chronology of biological processes among species pose significant challenges to translating pre-clinical results to humans (3).

Murata et al. (4) found high degrees of correlation with tissue histopathological specimens, using the first generation of the time-domain OCT system. Not surprising was the finding of discrepancies among methods. First, the coregistration between OCT images and histological cross sections is a challenging process in itself. The gold-standard method, histopathology, also has limitations that must be acknowledged. Currently, the most frequently used method consists of embedding the sample in plastic followed by different sectioning techniques. Tissue loss is significant with the saw and grinding technique, whereas sectioning artifacts, such as folding, are more frequent with the rotary microtome technique (6). The operational characteristics and physics of the first generation time-domain OCT system used in the Murata et al. study (4) also have limitations. The small profile (0.019-inch) of the ImageWire (LightLab Imaging Inc., Westford, Massachusetts) makes it more prone to eccentric intraluminal position or angulation relative to the axis of the blood vessel, which may result in imaging artifacts and overestimation of the cross-sectional area. Another important factor that may affect the accuracy of OCT measurements is the image calibration (Z-offset) process. We have shown that a 1% change in the Z-offset value may introduce an ~14% error of area measurement. The calibration must be systematically corrected along the entire pullback and is best performed in a frame where the catheter is in direct contact with the vessel wall because the transparent sheath is not always well visualized.

The new frequency-domain OCT systems such as the C7 XR LightLab (LightLab Imaging Inc.) provide very rapid image sampling (100 frames/s), which allows pullback rates of up to 20 mm/s compared with maximum 3 mm/s with the previous generation of systems. One should expect that these enhanced imaging capabilities together with a large

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catheter profile having a more central intraluminal orientation will minimize the effects of cardiac motion and other artifacts. Obviously, the new frequency-domain OCT systems will need to be scrutinized in carefully conducted validation studies, such as the present one.

After analyzing ~3,000 struts, Murata et al. (4) demonstrated the ability of OCT to appropriately identify uncovered stent struts, which has been postulated as the best morphometric predictor of stent thrombosis (7). These are timely observations because the need for a robust in vivo surrogate imaging end point of arterial healing is mounting. The old controversy regarding the safety of DES in the setting of acute myocardial infarction (AMI) (8,9) is likely to continue because no single clinical study has been sufficiently powered to address the important question of DES thrombosis in AMI, and necropsy data carry a natural inclusion bias and limited sample size. The best available histopathological data on AMI DES thrombosis is limited to a few patients, with analysis of only a small number of cross sections per patient (10). Recently, we conducted 2 DES clinical trials using OCT as a primary imaging modality in the AMI population, OCTAMI (OCT-Acute Myocardial Infarction) (11) and HORIZONS-OCT (Harmonizing Outcomes with Revascularization and Stents in AMI) (12). The rate of uncovered struts ranged from 1% to 6% of total struts compared with much higher rates reported in histopathological data (10). The OCT data included a total of 50,000 struts analyzed at 0.06-mm intervals compared with a few hundred struts at 1- to 3-mm cross-sectional intervals assessed by histology (7). Of note, uncovered DES struts are heterogeneously distributed throughout the stent, and their accurate quantification requires higher analysis sampling rates (13). Most importantly, the aforementioned OCT findings of the low frequency of uncovered DES struts are in accordance with the favorable clinical outcomes reported in a recent meta-analysis (9) and a large randomized trial (14).

Stent malapposition is another important factor to consider in post-DES assessment because it has been related to stent thrombosis (15). There is a paucity of data on the histopathological assessment of malapposition, and this was not assessed in the current report. Tissue shrinkage and pressure fixation hinder histology’s ability to accurately quantify stent malapposition. Conversely, individual strut-level malapposition can be quantified by OCT in vivo and is apparently more accurate than intravascular ultrasound (16). In vivo imaging also offers the ability to perform serial analyses and differentiate persistent from acquired stent malapposition, which may have different mechanisms and prognoses (17).

Whether the gap in our understanding of vascular healing after DES would have been bridged much sooner had higher resolution in vivo imaging been previously available remains unknown. However, various contemporary device clinical trials are integrating OCT as a primary imaging tool and considering strut coverage and malapposition as important, if not primary, surrogate end points (12,18–23). As this report illustrates well, OCT represents a major advance in our interventional armamentarium, offering the clinician and the investigator a unique translational imaging tool. One should also expect histopathological techniques to evolve, offering better tissue preservation, higher sampling rates with 3-dimensional reconstruction (24), and perhaps identification of endothelial prothrombotic phenotypes (25). The present report provides signs of a brighter future for vascular biology investigations. However, future studies should focus on the complementary role rather than on comparison of methods because advanced histology techniques and in vivo high-resolution imaging synergistically provide the fundamental tools to fuel discoveries of novel cardiovascular drug and device therapies.

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