JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 2, NO. 5, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2009.03.006

EDITORIAL COMMENT

From a Foggy Sight to a Clear Vision*

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Claude Monet stated that he wanted as new as possible a view of the world.
("Monet, The Impressionist Eye"
Musée Marmottan, Paris-16E, February 2009) (1)

The ability to image the endovascular environment of human coronary arteries at a micron-scale resolution is fascinating. Optical coherence tomography (OCT) might fulfill our need for a "corrective lens" to see the intravascular world the way modern therapies demand (2). Compared with angioscopy, its color-coded intravascular light precursor limited by forward view, OCT provides complete visualization of the stent luminal surface in multiple cross-sections (Fig. 1), allowing accurate measurements at each strut level (3) and similar ability to detect intraluminal thrombus (4,5). Furthermore, OCT can differentiate between red and white large thrombus with high sensitivity and specificity by measuring attenuation of light within the tissue (6). However, discrimination between fibrin clot and a small amount of neointimal hyperplasia in arteries with stent struts accompanied by their characteristic blooming might be more challenging (7). We have learned from postmortem pathology studies that patients receiving drug-eluting stents (DES) might be at increased risk of late stent thrombosis (8). Although no cause-effect can be derived from such studies, these observations also suggested that these patients have a higher incidence of uncovered struts and fibrin deposition, raising concerns about delayed healing after DES as a mechanism of thrombosis.

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In this issue of *JACC: Cardiovascular Interventions*, Otake et al. (9) extended these observations by using OCT to demonstrate a link between asymmetric stent expansion, percentage of uncovered stent struts 6 months after the implantation of sirolimus-eluting stent (SES), and local thrombus deposition. Importantly, the present study also supports the notion that vascular response to DES cannot be fully appreciated by measuring neointimal hyperplasia at a cross-sectional level, as has long been performed in intravascular ultrasound methodology. Healing heterogeneity is common after DES and can vary between different segments as well as between struts in the same cross-section of the arterial wall. The current observation that eccentric stent expansion is a risk factor for local thrombus formation makes sense, because asymmetry might lead to uneven strut spacing with higher drug concentrations being delivered where struts are clustered, potentially delaying healing in those areas (10,11). Because stent asymmetry is an extremely common finding and drug retention at tissue level is dependent on specific properties (hydrophilic vs. hydrophobic) of each drug and tissue (12), it is difficult to speculate on the clinical impact of slight stent asymmetry. A more careful look at the data will reveal that the authors appropriately did not claim that thrombus formed at sites of strut asymmetry or uncovered struts, because such statements would require more detailed analysis and a much larger sample size. Their data simply suggest that such patients were more likely to have thrombus somewhere in the stented segment. As expected, their additional findings confirmed the relationship between stent length and the risk of delayed healing. Given the common heterogeneity in plaque composition and distribution that characterizes longer lesions, longer SES might be more often suboptimally deployed, incompletely apposed and covered. Suboptimal technique is indeed a major predictor of both early and late thrombosis after DES deployment (13), highlighting the importance of mechanical factors in addition to biology as a determinant of vascular response. The fact that none of the 53 patients in the study by Otake et al. (9) developed stent thrombosis or adverse thrombotic coronary events despite a high percentage of local thrombus deposition at OCT deserves additional comment. First, the discordance between OCT findings and clinical events is neither reassuring nor discouraging, given the small sample size and short duration of the follow-up. The relationship between these OCT observations and subsequent clinical events has to be determined in a larger number of stents/patients and with additional years of clinical follow-up. The seminal work of Otake et al. (9) certainly encourages us to proceed in our search for better in vivo detection of different mechanisms of DES late thrombosis.

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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MAY 2009:467–9

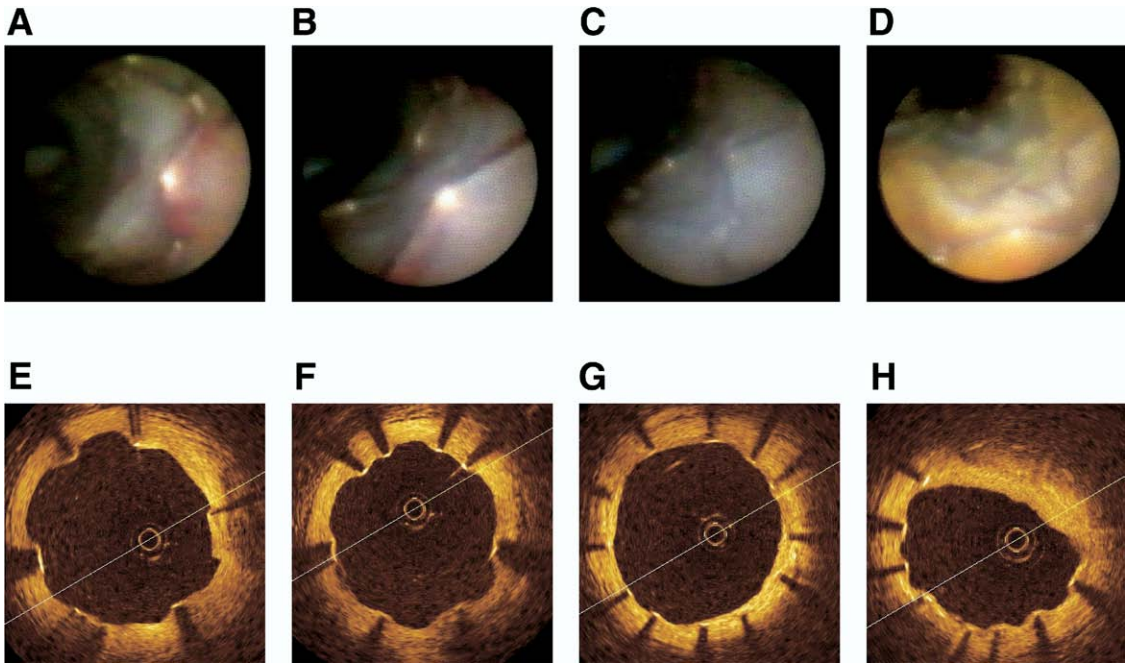

Figure 1. Coronary Angioscopy and Optical Coherence Tomography at Corresponding Cross Sections of a Sirolimus-Eluting Stent at Different Time Points After Implant

(A to D) Coronary angioscopy at 8 months. Details on shiny appearance of the stent struts with remaining thrombus **(A,B)**, thin coverage **(C)**, and underlying yellow plaque with tissue protrusion **(D)**. Due to the forward view not all images allow a complete lumen visualization. Optical coherence tomography at 5-year follow-up **(E to H)**. All tomographic views allow complete strut-level quantitative analysis.

Secondly, this study calls for an accurate revision of the OCT qualitative criteria for thrombus identification, particularly in the chronic phase of stent vascular healing. Usually, the accuracy of qualitative criteria (thrombus presence/absence) is subject to the application of thresholds to distinguish between different tissue entities. For instance, old (organized) thrombus has a smooth surface with a gradual decrease in light attenuation. However, the application of such criteria when differentiating between thrombus and neointima is less obvious in stented vessels, because it is limited to whether a sharp intensity gap exists between small protruding masses and neointima. In the case of a small amount of neointima, it is almost impossible to visually differentiate between a small amount of thrombus (fibrin deposit) and smooth muscle cell proliferation because of stent strut blooming. Unfortunately, our experience in >300 consecutive blind analyses of various DES platforms revealed that many cases might fall under this uncertain scenario, particularly when the core lab analyst is truly blind to the clinical status of the patient and stent assignments. These uncertainties between distinct entities might also explain the relatively high rate of local thrombus detection without adverse clinical events, especially considering that SES were likely deployed with optimal technique with a low frequency of malapposition. Whether OCT is indeed too sensitive and detects any minor transient fibrin or thrombus deposition that might occur as the result of intravascular manipulation rather than a permanent and progressive biologic response also remains to be defined. Hence, our group has taken a more conservative approach in dealing with intraluminal "thrombus-like" OCT images and considered it under a more general description of "abnormal intraluminal tissue" (AIT), which can be distributed in different categories on the basis of their relationship with covered versus uncovered and apposed versus malapposed struts. The AIT can be further categorized on the basis of the severely occlusive (restenosis) or nonocclusive nature of underlying intimal hyperplasia, because its mechanisms might vary (14). It is likely that these definitions will change in the future as a larger volume of patients with long-term follow-up becomes available, which will hopefully provide robust clinical end points to allow distinction between "malignant" AIT or thrombus and benign "AIT." Furthermore, semi-automated tissue classification algorithms will soon become available, which should decrease our current subjectivity regarding thrombus assessment.

Caution must be used in extrapolating the real frequency of subclinical thrombus formation in DES from the data of Otake et al. (9), considering the small number of stents and the fact that approximately 20% of the patients were

excluded from the analysis due to incomplete image acquisition. These concerns are part of the scientific debate and should not distract us from recognizing an important message from the work of Otake et al. (9), because it reinforces the need for significant improvements in stent geometry of DES platforms to have a more predictable mechanical and biological response in complex coronary lesions. One might expect—although not specifically addressed in this article—that different DES design might have different strut distribution and possibly tissue responses in various coronary geometries, as already suggested by measuring the angle between stent struts in a phantom model (15). Could OCT help to optimize stent technology? One might foresee that OCT could contribute at various stages of DES assessment, optimizing stent design evaluation and stent deployment techniques, quantifying the degree of stent coverage, and evaluating the mechanisms of delayed healing and thrombus formation at the strut level (16). Ultimately, the optimal use of a novel technology requires understanding not only of its potential but also of its limitations. Current OCT systems use occlusion of the coronary artery by a balloon catheter and distal selective coronary flushing for imaging. Alternatively, a non-occlusive technique might be used with a high flush rate only in relatively short segments, to avoid intracoronary fluid overload (17). Second-generation frequency domain OCT systems have been developed and will potentially overcome many of these practical limitations (2), allowing us to image a long (6-cm) stented coronary segment in a matter of a few (<5) seconds with a very small amount of contrast and perhaps superior image quality, without requirement of balloon occlusion. However, changing practice paradigms is not an easy task and will require much more than beautiful eye-catching images. From the age of 72 years, Monet had begun to suffer the effects of a cataract, which darkened his vision, a tragedy for this painter who loved light. For more than 10 years Monet refused to have the operation, fearing that it might alter his perception. He finally agreed to the operation, which proved successful and suddenly gave him a clarity of vision he had never experienced before. Optical coherence tomography was first tested in the retina (18) and could have helped an early and accurate diagnosis of Monet's sight problems, if available at that time. Nowadays advanced OCT is ready for primary clinical use. Through its use, we will need to learn again how the endovascular environment looks, a challenge even for Monet in his own words: "*The first look at the subject,*" he stressed, "*was always the truest, the most faithful*" (1). Meanwhile, interventional cardiologists will continue to explore the capabilities and limitations of OCT technology and help make the medical community appreciate that it is possible to see and understand what we have been doing to the vessel walls of our patients.

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Key Words: drug-eluting stents ■ optical coherence tomography ■ thrombosis ■ stent coverage.