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EDITORIAL COMMENT

Searching Between the Plaques Layers to Understand the Past and Predict the Future*

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The layers of the earth and the fossils hidden within the rocks reveal to the geologist the secrets of the past, sending him back for a trip millions of years long. Pathologists and nowadays cardiologists try to do the same, interrogating the vessel wall and atherosclerotic plaques, looking for the missing pieces of the complex puzzle that determine the pathophysiology of myocardial infarction and sudden death.

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Tian et al. (1) should be congratulated for their effort to collect new insights on the "in vivo" anatomy of coronary lesions, using a complex approach combining intravascular ultrasound and optical coherence tomography (OCT) to interrogate multiple vessels at the same time point.

The concept that a large superficial necrotic-lipid pool, barely protected by a thin fibrous cap, is a sign of plaque vulnerability, is now firmly established (2). What still remains unclear is the reason why some plaques ruptures occur without causing a clinical event. Tian et al. (1) addressed this issue comparing culprit lesions with rupture of the plaque (ruptured culprit plaque [RCP]), causing acute coronary syndrome, to plaque rupture, which remained silent (ruptured nonculprit plaque [RNCP]). Vulnerable plaques with a thin-cap fibroatheroma served as a control arm. RCP had a significantly smaller lumen area compared to RNCP, and the plaque burden was found to be significantly larger. The fibrous cap thickness <52 μm had good performance in discriminating ruptured plaque from plaques with thin-cap fibroatheroma.

These concepts broaden our knowledge on the genesis of acute coronary syndromes (ACS), we have so far collected. Plaque rupture causes an acute event when the residual lumen is not large enough to host the thrombus, the final event of the chain leading to ACS, and the blood flow is insufficient for cell survival. Of note, RCP exhibited an angiographic percentage diameter stenosis of 72% and an intravascular ultrasound minimal lumen area of 2.1 mm^2, over 2 times less than that found in RNCP (4.6 mm^2). Lumen narrowing obviously occurs in presence of a large plaque burden when the vessel remodeling ceases to offer a compensatory mechanism.

These in vivo observations confirm some of the conclusions recently reached by a histological study (3) and should be waived with optimism. The lumen area is easy to detect and this simple criterion may be used in the future to dichotomize the thin cap atheroma lesions that can rupture and cause ACS, from those that will not cause coronary events. These data are also in line with the findings from PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) (4), a prospective multicenter study that stressed the role of plaque burden and minimal lumen area in determining major acute events. Importantly, unlike the PROSPECT study, which included in the combined major endpoint the target vessel revascularization (likely due to plaque progression), Tian et al. (1) focused only on the occurrence of ACS, and therefore were able to link these anatomical features to the occurrence of major clinical events related to plaque instability.

The most used cutoff value to indicate a thin fibrous cap is 65 μm and derives from autopsy reports, but the thickness value that should be adopted for in vivo assessment is still a matter of dispute. Consistent with other reports (5), a smaller fibrous cap thickness was found by Tian et al. (1) in the groups with plaque rupture (43 μm for RCP, 41 μm for RNCP, and 56 μm for plaques with a thin-cap fibroatheroma), proving that fibrous cap overlying lipid plaque should reach a critical level before rupture. However, no differences in the thickness of the fibrous cap were appreciated between the 2 groups with plaque rupture (RCP and RNCP).

What We Still Don't Know

If we regard the glass as being half empty, we have to admit that the road to arrive at a comprehensive understanding of the mechanism of ACS is still long. In fact, over 30% of coronary events are not due to plaque rupture (2,6), and merely anatomical characteristics do not provide sufficient explanations. In this instance it is very difficult to understand the genesis of thrombus formation and identify the sites where it will occur.

Unlike intravascular ultrasound, OCT can depict fresh thrombus (7), a key element to identify culprit plaques. However presence of old, organized thrombus is still a challenge for intracoronary imaging modalities, including OCT. As revealed by anecdotic cases, during the process of

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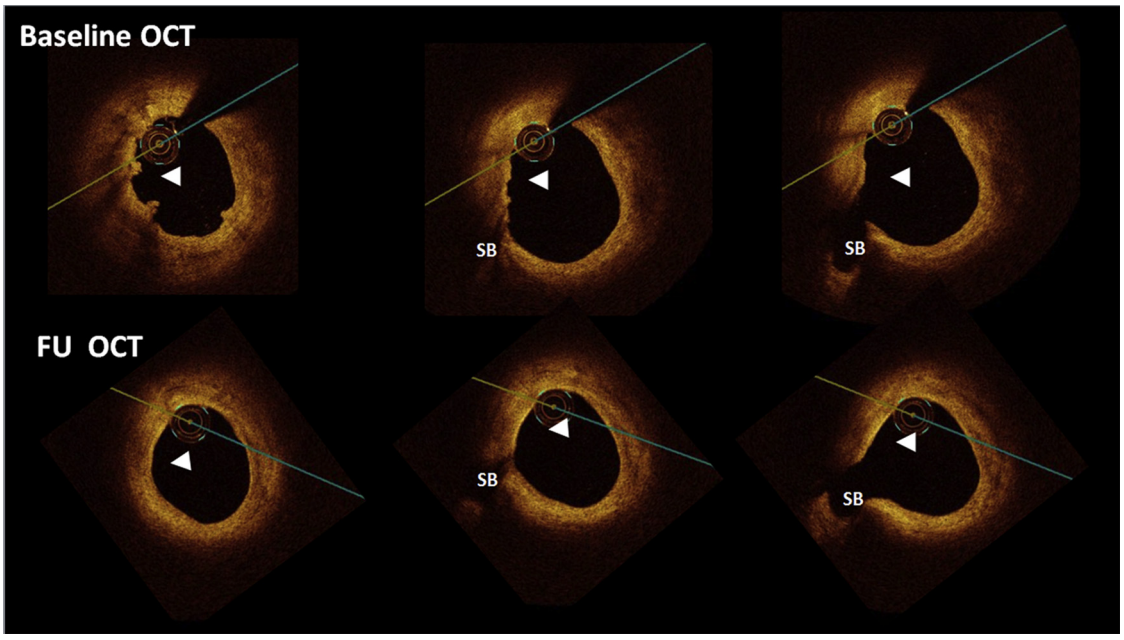

Figure 1 **Serial Changes in Culprit Plaque Composition**

Example of plaque healing after an acute coronary syndrome due to plaque erosion in a patient treated with thrombus removal without angioplasty. The **upper panel** shows frequency domain optical coherence tomography (OCT) images obtained after manual thrombus aspiration and subsequent local drug delivery of abciximab using a porous balloon at a physiologic pressure (Clearway, Atrium Medical Co., Hudson, New York). A small amount of fresh residual thrombus **(arrowheads)**, showing an irregular inner contour, was appreciated in the 3 cross sections obtained along a length of 1 mm, immediately before and at the takeoff of a small side branch (SB). The lower panels show the OCT appearance of the same sites after 9 months. It is almost impossible to recognize a coronary site with previous acute thrombosis **(arrowheads)** as the organized thrombus evolved to be homogeneous and smooth. FU = follow up.

thrombus organization, the irregular surface visible in the acute phase turns into a regular smooth contour, with the tissue appearance at OCT resembling that of fibrous tissue (Fig. 1). This sounds as a limitation for studies carried on with OCT. Tian et al. (1) compared ruptured plaques (culprit or nonculprit) with those that did not undergo rupture. This is certainly a step forward, in the effort to identify the plaques that at a certain point sustain a phase of instability. However, the ideal solution to dichotomize lesions that had a phase of instability versus the quiescent ones would rest in the identification of plaques that develop a thrombus at a certain time point, due to plaque ulceration or alternatively plaque erosion.

Plaque rupture can also be easily identified using OCT. In the present study plaque rupture was documented in 25% of cases at the RNCP sites, a figure consistent with previous data provided by the literature. Surprisingly, Tian et al. (1) reported a high incidence of thrombus formation (63%), a figure that could have been overestimated due to the already discussed limitations of OCT to address organized thrombus. It is likely that plaque ulceration without superimposed fresh thrombus indicates old events that occurred months or years before the OCT study (8). The fate of such lesions is not yet known and prospective data are needed to confirm their stability over time.

There is large consensus on the role of systemic inflammation in triggering ACS. Plaque rupture is biologically driven by inflammatory cells (lymphocytes, monocytes, macrophages, and later on foam cells), and inflammatory mediators. However, the impact of local inflammation remains a controversial issue. Its detection with intracoronary imaging modalities is a difficult task, possibly because they address only anatomical features, inferring on biochemical ones. OCT has a resolution that enables the identification of macrophage clusters. However, dedicated software should be adopted for off-line post processing of OCT images to improve the visual "eyeballing" assessment (7). The methodology adopted by Tian et al. (1) in this regard does not seem robust enough, with the majority of data obtained with the former time-domain technology, which provides images with a lower resolution in comparison with the present frequency-domain system. Of note, no differences were reported by Tian et al. (1) for the local sign of inflammation between the 3 lesion groups (RCP, RNCP, thin-cap fibroatheroma). This finding is in contrast with the conclusions of Narula et al. (3), who showed in a histological study a significant inflammatory gradient among disrupted plaques, vulnerable plaques with thin-cap fibroatheroma, and stable plaques.

The Future of Coronary Imaging

Despite the high definition of OCT images, the differential diagnosis between the fibrous cap overlying a lipid pool versus a band of clustered superficial macrophages may be difficult, given the similarities in optical properties. In the next future cardiologist should design prospective studies, combining OCT with other imaging techniques in a single probe. Combination of OCT with intravascular ultrasound or near-infrared spectroscopy will provide a more comprehensive evaluation helping to distinguish plaque components. Another unmet need is a better understanding of the biological characteristics of atherosclerosis and plaque instability. Molecular imaging strategies are a promising tool to accomplish this task and the development of catheters combining in vivo near-infrared fluorescence with intravascular ultrasound or OCT probe (9) seems a reasonable solution.

By discovering acute, recent, or old events, hidden inside the atherosclerotic architecture, imaging modalities can reconstruct some pieces of a single individual story. These studies will further increase our knowledge on how atherosclerotic plaques grow and cause ischemic events. Perhaps cardiologists are getting as clever and resourceful as geologists.

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