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EDITORIAL COMMENT

Clinical Imaging of ACS With Ruptured or Intact Fibrous Caps*

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PRE-PCI, OCT-BASED CHARACTERIZATION OF CULPRIT PLAQUES IN STEMI

In vivo intravascular imaging of culprit plaques in acute coronary syndrome (ACS) may shed light on the plaque substrate of acute thrombosis, either a ruptured fibrous cap (RFC) or an intact fibrous cap (IFC). This may help to unravel mechanisms of acute coronary thrombosis in ACS, monitor plaque healing after an acute event, and revisit indications for interventional treatments, in particular, stenting.

The OCTAVIA (Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty) study is an interventional phase 4 trial that enrolled 140 ST-segment elevation myocardial infarction (STEMI) patients (70 male and 70 female) according to pre-defined criteria. Patients with STEMI underwent quantitative coronary angiography, thrombus aspiration, post-aspiration optical coherence tomography (OCT) to investigate the morphology of the culprit plaque, everolimus-eluting stenting of the culprit lesion (independent of the culprit plaque morphology), post-stenting OCT, and further quantitative angiography in the short- and long-term follow-up. The primary outcome measures were the percentage of RFCs and IFCs at the infarct-related lesion and the assessment of sex differences as assessed by OCT. The coprimary endpoint was the evaluation of the percentage of covered stent struts by OCT in the infarct-related lesion at 9 months in RFC lesions and IFC lesions 9 months after treatment. Further aims were the comparative evaluation of biomarkers in RFCs versus IFCs and the analysis of the aspirated material.

OCT CONFIRMS THE PREVALENCE OF DIFFERENT PLAQUE SUBSTRATES TRIGGERING ACUTE THROMBOSIS IN AMI

Autopsy studies have shown that acute myocardial infarction (AMI) is caused by the acute thrombotic occlusion of an epicardial coronary artery (1); coronary dissections may cause AMI in a minority of cases (2). Acute coronary thrombosis occurs with coronary plaque rupture in ~75% of AMI and plaque erosion in the remaining 25% (3). These proportions are somewhat similar in AMI and sudden coronary death (4). In vivo intracoronary OCT-based imaging has confirmed the proportion of both rupture and erosion described in autopsy series (5,6). Such clinical imaging studies have validated the pathological findings and have contributed to the characterization of vulnerable plaques prone to rupture, including superficial plaque inflammation (7) and erosion in which the pathological substrate increases local thrombogenic potential (8). Other findings, including superficial calcific nodules as substrates of acute coronary thrombosis in AMI (9,10) and a higher prevalence of plaque erosion in females than in males (3,4), have not been confirmed in vivo.

Pathological diagnosis of cap rupture describes a plaque characterized by a thin-cap fibroatheroma with loss of continuity of the cap, whereas erosion describes a condition in which the thrombus forms on either a fibrous plaque or a fibroatheroma with a thick cap. The OCT diagnosis of plaque rupture and erosion in an acute event reproduces the pathological findings and is based on the evidence of thrombus occurring on a ruptured fibrous cap and an empty core cavity versus preserved fibrous cap integrity in an acute event with an intact fibrous cap, respectively (11). In the OCTAVIA study, although plaque rupture and erosion are structurally different, the final effect

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appears to be similar, making treatment the same, even though the underlying mechanisms of platelet adherence and thrombus generation may be different (12,13).

THE OCTAVIA TRIAL RESULTS IN STEMI

The primary outcome measures and related results reported by Saia et al. (14) in this issue of *iJACC* are part of the OCTAVIA trial and demonstrated that: 1) an IFC was the plaque substrate for acute coronary thrombosis in approximately one-third of cases; 2) as assessed by OCT, the prevalence of IFCs was similar in male and female patients, not confirming the higher prevalence of IFCs noted in females in the autopsy studies; 3) there was no difference in the extent of covered stent struts by OCT in infarct-related lesions

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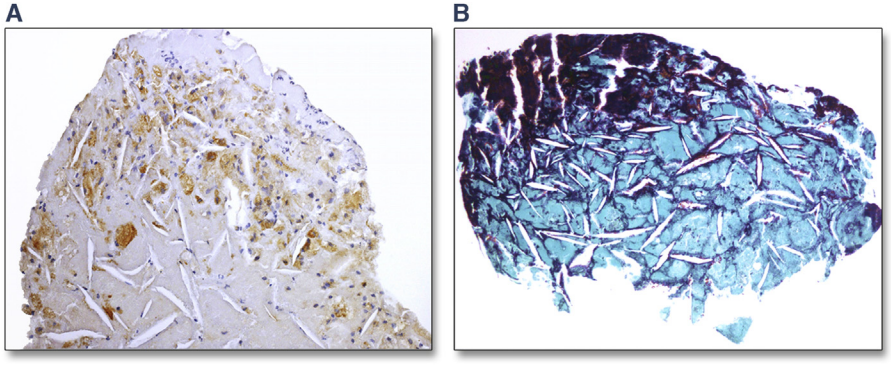
at 9 months regardless of the plaque substrate, either RFC or IFC; and 4) the morphology of the culprit plaque was not associated with any specific clinical features or biological markers. The levels of high-sensitivity C-reactive protein, eosinophil cationic protein, thromboxane B_2, and myeloperoxidase were similar, and the immunohistochemical study of aspirated material obtained from RFC and IFC substrate showed similar myeloperoxidase- and CD68-positive cells, as well as a similar CD42b score.

CLINICAL IMPLICATIONS OF THE STUDY

The observation that acute and chronic vascular response to percutaneous coronary intervention (PCI) with current generation of everolimus-eluting stents happened to be similar in patients with IFCs and RFCs seems to indicate a limited clinical role for pre-interventional characterization of the plaque substrate in ACS. However, this finding has been a matter of controversy, as in the past few years, emerging OCT-based studies (5,15) highlighted the possibility of stenting RFC plaques and not stenting IFC plaques while maintaining aggressive antiplatelet treatment after manual thrombus aspiration or thrombolysis-mediated dissolution. The local healing response to PCI, similar for both RFC and IFC plaques in the OCTAVIA study (14), may be explained either by heavy platelet inhibition that provides protection against any ACS plaque morphology where platelets are involved or the fact that stents produce the same local healing response in coronary arteries, which may be independent of the local pathology. Similar morphology of local healing does not necessarily equate to identical treatment. Is it also possible that knowing local plaque characteristics before the intervention may benefit IFCs with a tight lesion and may predict embolic rates and slow flow in RFCs?

Additionally, the observation that 75% of IFC plaques versus 100% of RFC plaques were lipid rich may suggest a better imaging-based definition of a pultaceous core in plaques with IFC, where hemorrhagic invasion of the core did not occur. An important finding of the study (14) is the characterization of plaque material in the RFC (23 of 42, 54.8%) compared with the IFC (1 of 13, 7.7%). Aspiration of the material occluding the coronary lumen at the culprit site in plaques with RFCs may extract cap

FIGURE 1 Samples of Aspirated Material From Atherosclerotic Plaques in AMI Patients



(A) A sample that has been immunostained with anti-CD68 antibodies. The sample contains foamy macrophages **(brown)** and cholesterol clefts, which are undoubtedly originating from a ruptured fibro-fatty plaque. **(B)** A MOVAT pentachrome–stained sample from the material aspirated in the culprit lesion of a patient with acute myocardial infarction. The sample shows pultaceous cholesterol cleft-rich material, which undoubtedly originates from a ruptured core-rich plaque.

fragments and/or necrotic core debris (**Figure 1**). The post-aspiration OCT images reveal empty cores delimited by the fibrous strands of the residual cap and by the empty crater of the plaque core; the ruptured fibrous cap OCT panel of Figure 1 in Saia et al. (14) shows a typical view of an empty core in a ruptured plaque. OCT studies have contributed to unraveling the mechanisms of plaque healing after dissolution of the acute thrombus with and without stent implantation (5,15). Although in RFCs, the thrombogenic collagen substrate of the internal layers of the fibrous capsule may remain exposed even after aspiration, the risk of recurrent thrombotic events is likely prevented by the antiplatelet treatment that staves off thrombosis during the healing and re-endothelialization phase. The study by Saia et al. (14) found plaque material, similar to samples from RFCs, from only 1 IFC event, thus indicating that either the aspiration procedure itself ruptured an intact cap or OCT did not correctly recognize an RFC.

Numerous imaging studies, including the present one, are providing evidence of the feasibility of in vivo pre-PCI intravascular diagnostics and post-procedural monitoring of the treatments of the culprit plaque in ACS. Solutions other than stenting could be matter of consideration when treating plaques that show low structural vulnerability, such as those with IFCs, high Thrombolysis In Myocardial Infarction flow grade and small plaque burden after effective thrombus aspiration.

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