New Morphological Insights on Coronary Plaque Rupture

Bridging the Gap From Anatomy to Clinical Presentation?*

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Acute coronary syndromes (ACS) present as ST-segment elevation myocardial infarction (STEMI) or as non–ST-segment elevation acute coronary syndrome (NSTEMI). This simple “early” clinical classification has major therapeutic implications as it determines the requirement for urgent reperfusion. Subsequent clinical outcome will eventually separate NSTEMI patients into those actually suffering from myocardial infarction (NSTEMI) and those with unstable angina. In most cases, however, the underlying pathological substrate appears to be identical: the rupture of a “vulnerable” plaque with concomitant intra-coronary thrombosis (1–3). Thin-cap fibroatheroma (TCFA) is accepted as the most frequent guilty substrate (1–3). However, the reason(s) explaining why this uniform pathological substrate may cause widely diverse clinical presentations remains poorly understood.

Classical thought suggests that the extent, content, and dynamic behavior of the associated thrombus constitutes the main determinant of the resulting clinical picture. According to the prevailing paradigm, thrombi causing a complete and sustained vessel occlusion generate STEMI, whereas those inducing incomplete or transient vessel occlusion result in NSTEMI (1–3). Other players in the field such as total plaque burden, vessel spasm, and the thrombogenic milieu may have just a modulating role (1–3). However, what factors determine the occurrence of complete/sustained thrombotic vessel occlusions leading to STEMI?

In this issue of JACC: Cardiovascular Interventions, Ino et al. (4) address this important question using optical coherence tomography (OCT) to unravel subtle morphological differences in culprit lesions of patients presenting with STEMI and NSTEMI. They found that the incidence of plaque rupture, TCFA, and red thrombus was significantly higher in STEMI patients. Furthermore, in these patients, the area of the ruptured cavity was larger and its opening was more frequently oriented against the direction of coronary flow (4). These novel findings provide a unique opportunity to revisit current knowledge on plaque rupture and its related clinical consequences.

Anatomic Insights Gauged From Intracoronary Diagnostic Techniques

All intravascular imaging modalities, including intravascular ultrasound (IVUS), virtual histology, coronary angiography, and OCT, have demonstrated striking morphological differences between patients with stable angina and those with ACS. However, the identification of distinct features able to separate ACS patients according to clinical presentation has proved to be elusive. On IVUS, complex, positively remodeled, soft plaques represent the fingerprint of ACS (5–9). Remodeling phenomena and ruptured plaques appear to be more prevalent in STEMI patients but available evidence remains inconclusive. Hong et al. (5) demonstrated that ruptured plaques in the infarct-related lesion were equally frequent in STEMI and NSTEMI patients. Besides, STEMI patients with plaque rupture show a higher incidence of soft plaques, positive remodeling, no-reflow, higher creatine-kinase levels, and lower ejection fraction (6).

Similarly, in ACS patients undergoing interventions, the presence of necrotic core on virtual histology has been related with markers of distal embolization (7). Axial location of plaque rupture, however, was not analyzed in those previous studies (5–7). Other IVUS studies suggested that “proximal” ruptures were more frequently detected in culprit lesions of patients with ACS than in non-ACS patients (8). Volumetric analysis (9) described ruptured plaque characteristics, but rupture location was not related with clinical presentation.

Because of inadequate resolution, IVUS and virtual histology correlates of plaque erosion remain unsettled. Likewise, with these techniques, a reliable analysis of thrombus content is very difficult and differences in thrombus characteristics among ACS patients have not been demonstrated (5–9).

Coronary angiography, however, has been specifically used to differentiate ACS patients according to clinical presentation. Complex and ruptured yellow plaques are equally prevalent across all types of ACS (10–12). However, most patients suffering STEMI typically have reddish thrombi, whereas those with unstable angina frequently have grayish-white thrombi (10). Likewise, occlusive thrombi are rare in unstable angina but these are systematically visualized after STEMI (10). Red and occlusive thrombi are also more
prevalent in patients with post-infarction angina than in other subsets of unstable angina (12). Furthermore, in STEMI patients undergoing late, elective, interventions for occluded vessels, the **persistence** of an occlusive red thrombus is visualized in 90% of cases (11).

**Classic Pathological Findings**

Plaque rupture or erosion with superimposed thrombus is the pathological hallmark of ACS (1–3). Fibrous caps are thinnest and macrophage and T-cell infiltrated at the site of rupture, which is more frequent at the shoulder region of the plaque in patients dying suddenly at rest (1–3). Pathological studies with section carried out at 2- to 3-mm intervals or longitudinally showed that plaque ruptures occur more frequently at the site of severe narrowing or distal to it (13,14) (Fig. 1). These findings suggest that plaque rupture occurs at low shear regions. At the site of rupture there is always a platelet-rich thrombus (white thrombus), and when there is a total occlusion, there is always a propagated thrombus, which is rich in red blood cells (red thrombus), proximal and distal to the site of rupture (1–3,13,14). However, pathological analyses frequently lumped together all clinical faces of ACS. In fact, no pathological report has suggested potential differences in plaque characteristics between STEMI and NSTEMI patients. The lack of practical interest in this “early” clinical classification from a pathological perspective (where extent, distribution, and transmurality of myocardial damage are accurately established) may be implicated. Moreover, adequate longitudinal reconstruction of the coronary arteries from autopsy specimens is very challenging and most pathological examinations actually rely on multiple cross-sectional analyses (3). However, the validity of these previous histological findings—obtained in experienced laboratories—is indisputable and strongly suggests that most plaque ruptures occur either at sites of maximal narrowing or just distal to them (13,14).

**Present Study**

Ito et al. (4) used OCT to examine the culprit lesions of 89 consecutive ACS patients (40 STEMI, 49 NSTEMI). The incidence of plaque rupture, lipid-rich plaque, and TCFA was significantly higher in STEMI patients who also had thinner fibrous caps. Thrombus and, in particular, red

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**Figure 1. Thrombus Propagation in Plaque Rupture**

(A) Composite of a longitudinal section of a left anterior descending coronary artery with plaque rupture: the rupture site is marked by the **yellow arrowhead** (Movat pentachrome). (B) The same longitudinal section as in A stained with Carstairs method for the detection of fibrin and red cells (dark red) and platelets (blue-gray). (C) The proximal thrombus consists predominantly of red cells and layers of platelets (red thrombus), whereas the site of rupture is platelet rich (white thrombus) (staining by antibody to glycoprotein Illa). Reprinted, with permission, from Virmani et al. (14). LAD = left anterior descending; LD = left diagonal.
thrombus were more prevalent in this cohort (4). In concordance with prior angioscopic reports (10), the present study confirms the dramatic correlation between thrombus type and clinical presentation. Furthermore, the morphology of plaques also differed according to clinical presentation. First, the “ruptured cavity” was significantly larger after STEMI. Second, its aperture was more frequently located “against” the direction of coronary flow in these patients (4). However, some aspects of the present investigation deserve special consideration.

First, mechanical aspiration of thrombus before intervention has been demonstrated to be of clinical value in STEMI patients. However, the use of relatively bulky (5.1-F) aspiration catheters is a matter of concern when subsequent, detailed analyses of plaque morphology are attempted (4). This strategy not only hampers a comprehensive evaluation of the associated thrombus but also might induce significant changes in plaque morphology (Dotter effect). Considering that thrombus-removal catheters were more frequently employed in STEMI patients, one wonders whether this maneuver might have modified the underlying plaque including the appearance, location, and orientation of the rupture site, or even induced “proximal type” ruptures. Interestingly, although angiographic lesion severity was greater in STEMI patients, OCT-derived minimal lumen area was similar in both groups (4). Thrombus aspiration would create a vacuum that is likely to disturb the plaque as no necrotic core could be identified by OCT but just a cavity (ulcerated lesion), which we have not observed in pathological studies of coronary arteries with luminal thrombi that have not been intervened (1–3). Likewise, if a larger thrombus burden was aspirated in STEMI patients, this could help to explain the larger rupture cavity in this patient subset. In this regard, data assessing the potential correlation between the aspirated material and OCT findings would have been of unique interest, but, unfortunately, the evacuated material was not analyzed (4). Furthermore, OCT-derived data on lesion length and distance from the rupture site to the smallest lumen area were not provided. Nevertheless, this report nicely complements a previous study by the same investigators (15) where the maximum aperture of the rupture plaque was carefully analyzed (before “any” intervention) in longitudinally reconstructed IVUS images. In that study (15), plaques with rupture at the proximal shoulder were also more frequently detected in STEMI patients, even after adjusting for potential confounders. Therefore, the growing body of comprehensive evidence built by these investigators (4,15) is highly reassuring and robust enough to suggest distinct and unique morphological plaque differences between STEMI and NSTEACS.

Second, the lack of data on alternative ACS pathological substrates, including plaque erosion, calcified nodules, or intraplaque hemorrhage was unexpected (4). Plaque erosion may explain up to one-third of cases with ACS, particularly in women and younger patients (1–3). In a previous OCT study by the same group (16), fibrous cap erosion was detected in 23% of patients with acute myocardial infarction. Notably, in that study (16), the ability to recognize this challenging and elusive entity was considered a major advantage of OCT compared with IVUS.

Third, despite its unique spatial resolution, OCT has some important caveats. Probably, its major limitation is that it represents a shotsighted technique that only provides information of the superficial layers of the vessel wall (16). Indeed, at diseased coronary segments, it is virtually impossible to identify the external elastic lamina contour. Therefore, in the current study, no absolute or relative measures of lipid pool area, total plaque burden, remodeling phenomena or thrombus size were provided, although these remain of critical interest from a pathophysiologic standpoint (5–9). Further studies simultaneously using these complementary tomographic techniques would be required to merge together OCT-derived high-resolution precise details on plaque surface characteristics with a global IVUS analysis of the extent and distribution of the entire plaque burden. In addition, red thrombus induces shadowing of distal structures, preventing their characterization, and this problem may be relevant when its presence is ubiquitous.

Finally, in this series, time-domain OCT with the occlusive technique and very slow pullback speed was used. Currently available frequency-domain OCT systems do not require vessel occlusion and are not only user-friendly but also provide a better image quality, deeper penetration, and faster acquisition, virtually allowing unrestricted interrogation of long coronary segments.

Conclusions

The present study suggests that distinct plaque morphological features differentiate patients presenting with STEMI and NSTEACS. In proximal-type ruptures, anterograde coronary flow may cause the residual plaque to “roll-up” back across the rupture site, further extending its aperture (4,15). The highly thrombogenic atherosclerotic core will be continuously exposed to flowing blood, resulting in progressive thrombus formation and, eventually, in definitive vessel closure. Proximal ruptures may also generate a “valve-like” mechanism that might contribute to their untoward fate. Conversely, in distal-type ruptures, coronary flow will reduce the aperture size and the plaque will be “relatively” protected against progression or thrombosis. This rupture location might even facilitate spontaneous vessel healing in a way similar to that seen in most nonflow-limiting, iatrogenically induced, distal dissections (17). Whether this mechanism might also explain asymptomatic episodes of plaque rupture remains speculative (18).
Further studies are warranted to elucidate which factors actually determine the occurrence of proximal versus distally located ruptures within a given vulnerable plaque. Additional information is eagerly required to close the gap between coronary anatomy and clinical presentation in order to devise adequate preventive therapeutic strategies aimed to avoid the feared consequences of plaque rupture.

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