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iVIEW

EDITOR'S PAGE

Napkin-Ring Necrotic Cores: Defining Circumferential Extent of Necrotic Cores in Unstable Plaques

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The culprit plaques associated with acute coronary events are huge and occupy a large area of the vascular cross section. These plaques typically contain large necrotic cores. Although these plaques are substantially large they are often positively remodelled and may not always compromise the luminal integrity. They are covered by a thin fibrous cap, which is inflamed with macrophages, and the smooth muscle cell content of the cap is scarce. The fibrous cap thickness in disrupted plaques has been reported as 23 ± 19 μm and more than 95% of the caps measure <65 μm in thickness. The plaques with histopathological characteristics similar to disrupted plaques but with an intact cap (and lack of an overlying luminal thrombus) are considered vulnerable to rupture; because the cap thickness is <65 μm such plaques have been referred to as thin-cap fibroatheromas (TCFA) (1,2).

The necrotic cores in culprit lesions have always been shown to occupy at least 10% of the plaque area in cross section. Necrotic core size is greater in the disrupted plaque compared with TCFA and occupies 34 ± 17% and 23 ± 17% of the plaque area, respectively. However, the length of the necrotic core is similar in ruptured and rupture-prone plaques, varying from 2 to 22 mm, with a mean of 9 and 8 mm. The pathologic observations dictate that instability is more closely associated with the circumferential extent of necrotic cores; at least three-fourths of the rupture-prone plaques involve >120° of vascular perimeter. Serial sections through the atherosclerotic lesions show the serpentine nature of necrotic cores, such that when it surfaces closer to the lumen it renders the plaques vulnerable to rupture.

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Assessment of necrotic core size and fibrous cap thickness best provide the morphologic markers of plaque instability. Numerous studies have reported the intravascular ultrasound (IVUS) characteristics of the culprit plaques in patients presenting with acute coronary events. However, to identify the features associated with future events, a prospective IVUS study followed angiographically <50% occlusive coronary lesions in more than 100 patients for 2 years (3). Twelve patients developed acute coronary events. The culprit lesions had exhibited larger percent plaque area (67 ± 9%) at the time of enrolment compared to plaques not associated with future events (57 ± 12%, $p < 0.05$); the lumen area was no different (6.7 ± 3.0 mm^2 vs. 7.5 ± 3.7 mm^2, respectively). Most importantly, the culprit plaques had originally contained shallow echolucent zones; uneventful plaques rarely revealed echolucence. The more recent PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study further confirmed the importance of shallow necrotic cores. In a follow up of 700 acute coronary syndrome patients with virtual histology–IVUS examination, presence of necrotic core adjacent to lumen (odds ratio: 3.0) emerged as one of the most significant independent predictors of future coronary events in nonintervened lesions. Although IVUS resolution is grossly inadequate, the shallow necrotic core should be representative of TCFA or a rupture-prone plaque.

The actual clinical assessment of fibrous cap thickness is feasible by an imaging modality of high resolution such as optical coherence tomography (OCT). Although no convincing prospective data are available correlating OCT-verified cap thickness and future coronary events, OCT examination of patients presenting with acute coronary syndrome has characterized culprit lesion as a lipid-rich plaque with cap

Table 1. Metrics of Computed Tomography Angiographic Low Attenuation Plaques Associated With Future Coronary Events

	ACS	No ACS	p Value	ACS 0–12 Months	ACS 12–24 Months	p Value
LAP volume (mm^2)						
Mean ± SE	3.2 ± 0.5	0.5 ± 0.2	<0.001	4.7 ± 0.51	2.0 ± 0.6	<0.001
95% CI	2.3–4.1	0.2–0.9		3.6–5.7	6.6–2.4	
LAP area/plaque area (%)						
Mean ± SE	21.4 ± 3.7	7.7 ± 1.5	<0.001	31.5 ± 4.5	8.1 ± 5.2	<0.001
95% CI	14.1–28.7	4.7–10.6		22.5–40.4	2.2–18.4	

Data from Motoyama et al. (6).
ACS = acute coronary syndromes; CI = confidence interval; LAP = low attenuation plaques.

thickness <65 μm. The average fibrous cap thickness was 47 μm in culprit lesions associated with acute infarction. On the other hand, in patients presenting with stable angina the average cap thickness was 102 μm (p = 0.03). OCT-verified lipid-rich plaques, defined as lipid occupying ≥2 quadrants of the cross-sectional vascular area (or 180° circumferential involvement), were observed in 90% of infarct patients (4).

Noninvasive assessment of rupture-prone coronary plaques has been primarily attempted by computed tomography (CT) angiographic characterization. Necrotic core rich plaques have been defined as low attenuation plaques with <30 HU density; low attenuation areas correlate closely with IVUS-verified echolucent zones (5). In a large prospective study, two CT angiographic plaque characteristics, low attenuation plaques (LAP) and positive remodelling (PR), were associated with subsequent development of acute coronary events. Of more than 1,000 enrolled subjects, 45 showed these 2 features; acute coronary events developed in 10 (22%) compared with 4 (0.5%) of the 820 patients with neither PR nor LAP. None of the 167 patients with normal angiograms sustained acute events (p < 0.001). PR and/or LAP were independent predictors of acute coronary events (hazard ratio: 23, 95% confidence interval: 7 to 75, p < 0.001) (6). Analyses of more than 10,000 coronary segments demonstrated significantly greater LAP volume and percent LAP/total plaque area of the eventful plaques compared with those not associated with future events (Table 1). Further, the LAP volume was greatest in the lesions that resulted in an acute event within the first year of follow-up compared to those who developed an event in the second year.

Although the fibrous cap thickness is an important morphological determinant of plaque instability, its identification is not possible by noninvasive imaging modalities. In the current issue of *iJACC*, Kashiwagi et al. (7) compare OCT and CT angiographic findings and propose that a ring-like attenuation in a CT angiographic cross section may be a surrogate marker of TCFA. In this study of 100 patients presenting with either acute coronary event or stable angina, the coronary lesions were divided into a TCFA and a non-TCFA group based on OCT findings. CT angiography-verified PR was observed more frequently in the TCFA (75%) than in the non-TCFA group (30%, p < 0.001). The TCFA group also demonstrated LAP more frequently; CT attenuation value in the TCFA group (35 ± 32 HU) was significantly lower than the non-TCFA group (62 ± 34 HU, p < 0.001). Most importantly, ring-like attenuation in the TCFA group was 11-fold higher than the non-TCFA group (44% vs. 4%, p < 0.0001).

The iPIX by Goldstein et al. (8) in this issue of *iJACC* offers complementary data employing near-infrared spectroscopy which identifies lipid-rich plaques. They convincingly propose that the presence of circumferentially extensive, ring-like necrotic core is usually associated with histologically-verified thin fibrous caps. These two studies presented in the current *iJACC* issue reconfirm the importance of circumferential extent of necrotic core in the plaque instability. Napkin-ring like necrotic cores should offer an indirect evidence of thin fibrous cap and this observation is likely to add specificity to the CT angiographic assessment of unstable plaques.

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