Insights from intravascular ultrasound on pathophysiology of acute coronary syndromes

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Abstract

Of the various thrombosis-prone morphologies, thin-capped fibroatheromas account for the majority of events. The rest are comprised of erosions and calcific nodules. Almost all IVUS analyses have either compared stable vs. unstable patients (or ruptured vs. nonruptured plaques) or have reported histopathologic-equivalent findings. While these approaches have limitations, there are important lessons. Greyscale IVUS features of thin-capped fibroatheromas include positive remodeling, hypoechoic plaque, spotty calcification, and attenuated plaque. Plaque rupture, the clinical expression of a vulnerable plaque, is detected in approximately 50-60% of culprit lesions in patients with acute coronary syndrome and in a variable percentage of secondary, non-culprit lesions. A ruptured plaque becomes symptomatic because of thrombus formation and lumen narrowing. Ruptured plaques occur in predictable sites in the coronary tree; however, greyscale IVUS does not have the ability to predict which vulnerable plaques are likely to rupture.

Key words: intravascular ultrasound, vulnerable plaque, plaque rupture, remodeling.

Introduction

Of the various thrombosis-prone morphologies, thin-capped fibroatheromas account for the majority (approximately 70%) of events [1, 2]. Thin-capped fibroatheromas are reported to have the following pathologic features: (1) positive remodeling, (2) a fibrous cap less than 100 microns (and perhaps less than 65 microns) at its minimum thickness, (3) a large lipid/necrotic core often containing hemorrhage and/or calcification, (4) speckled or diffuse calcification (not enough to increase plaque stability although the absence of any calcium is also rare in rupture-prone plaques), (5) abundant intra-plaque vasovasorum, and (6) macrophage infiltration of the thin fibrous cap [3-5]. The resolution of intravascular ultrasound (IVUS, 100-150 microns, at best, axially) limits its ability to detect and measure a rupture-prone thin fibrous cap – especially when this fibrous cap is intact and the trailing edge indistinguishable from the underlying plaque. Intravascular ultrasound cannot detect plaque inflammation. Without contrast injection, IVUS cannot detect vasovasorum.

The next most common thrombosis-prone morphology is an erosion. An erosion is, to some extent, a histopathologic diagnosis of exclusion [3-5]. There is no fibrous cap, positive remodeling is absent, and there is minimal inflammation. Other than the lack of positive remodeling, none

of the histopathologic features of erosions can be detected by IVUS.

A more rare type of vulnerable plaque is a superficial calcified nodule within or very close to the fibrous cap of the plaque that can protrude through to rupture the cap. It is readily detected by IVUS.

To date, only one IVUS study has attempted to predict plaque instability [6]. Instead, to study lesion characteristics that are associated with plaque vulnerability, almost all IVUS analyses have either (1) compared stable vs. unstable patients or ruptured vs. nonruptured plaques or (2) have reported histopathologic-equivalent findings. While these approaches have limitations, there are important lessons.

Remodeling

During the development and progression of atherosclerosis, the external elastic membrane (EEM) cross-sectional area (CSA) may increase; this is termed "positive" or "outward" or "expansive" remodeling, and (among other things) it limits the impact of plaque accumulation on lumen compromise. In positively remodeled lesions there can be a large plaque burden despite little lumen compromise (Figure 1); a large plaque burden should not be confused with a significant stenosis. Conversely, the EEM CSA may decrease; this has been termed "negative" or "inward" or "constrictive" remodeling, and it can contribute to stenosis formation apart from plaque accumulation.

However, IVUS assessments of remodeling in unstable lesions have been based on studies performed at a single point in time comparing the lesion to proximal and/or distal reference segments, not on serial (baseline and follow-up) analyses. (Static and serial assessment of coronary remodeling may be discordant; therefore, the two cannot be used interchangeably when evaluating lesion stability. [7]) A number of definitions of remodeling have been proposed (Figure 1):

- lesion EEM CSA/reference EEM CSA; if the lesion EEM CSA is greater than the reference EEM CSA (index > 1.0), there is positive remodeling; if the lesion EEM CSA is smaller than the reference EEM CSA (index < 1.0), there is intermediate/negative remodeling [8, 9];
- some authors set the above threshold higher to define positive remodeling as an index > 1.05, negative remodeling as an index < 0.95, and intermediate remodeling as an index between 0.95 and 1.05 [10];
- other authors have calculated a "theoretical interpolated" lesion EEM CSA based on the size of the proximal and distal reference EEM, tapering, and the axial location of the lesion relative to the two references; positive remodeling is a lesion EEM CSA greater than the "theoretical interpolated" EEM CSA [11, 12];
- Nishioka proposed the following classification: positive remodeling as a lesion EEM CSA greater than the proximal reference, negative remodeling as a lesion EEM CSA smaller than the distal reference, and intermediate remodeling as a lesion EEM CSA intermediate between the proximal and distal references [13].

One confusing aspect of these various definitions is that they can result in an individual lesion being classified as positive remodeling by one definition, but not by another one. This is because of (1) limitations resulting from reference site selection, reference site plaque burden, vessel tapering, etc.; (2) the fact that the reference segments have, themselves, undergone remodeling changes; and (3) the necessity to select a single lesion site cross-section for comparison with the reference segment while the remodeling index may vary along the length of the lesion. Nevertheless, assuming that consistent rules are followed, any one of these definitions is useful for studying populations or for assessing clinical-pathophysiologic correlations. Furthermore, lesions with the greatest positive or negative remodeling tend to be classified as such by all of the above definitions while the greatest disagreement occurs in lesions with intermediate remodeling (those with a remodeling index close to 1.0).

Positive remodeling in unstable lesions

In pathologic, angioscopic, radiofrequency-IVUS, and optical imaging studies, positive remodeling is strongly associated with unstable lesion morphologies. These have included plaque rupture, yellow plaque color, thrombus formation, presence and size of the lipid/necrotic core, and biomechanical lesion instability [5, 14-18]. There is also consistent IVUS data indicating that acute coronary syndrome (ACS) lesions more often have positive remodeling characteristics compared to either chronic stable angina lesions or to control plaques elsewhere in the coronary tree [10, 19-22]. Third, within the length of a single lesion, the site of plaque rupture has the largest remodeling index [23]. Finally, (1) positive remodeling has been associated with new lesion formation in patients with stable angina undergoing single vessel intervention [24]; (2) CK-MB elevation after percutaneous coronary intervention [25]; (3) no reflow in primary infarct angioplasty [26, 27]; (4) recurrent ischemia within one month after thrombolysis for acute myocardial infarction [28]; (5) target lesion revascularization in patients undergoing nonstent intervention [8]; (6) major adverse coronary events in patients with unstable angina undergoing any form of revascularization [29]; and (7) in-hospital complications and major adverse coronary events in patients with stable angina undergoing intervention [24]. Thus, the current cumulative evidence

indicates that positively remodeled lesions are more biologically active than intermediate or negatively remodeled lesions; and positive remodeling is a marker for future clinical instability.

Nevertheless, not all culprit lesions in ACS patients are positively remodeled; for example, the absence of positive remodeling in an acute setting may indicate that the culprit lesion morphology is one of plaque erosion rather than rupture, especially if there are no IVUS features of a ruptured plaque. There is evidence that diabetes mellitus and advanced patient age are associated with less positive remodeling [30, 31].

Plaque composition

Grey scale IVUS studies consistently show more hypoechoic plaque in lesions of ACS patients compared to patients with stable angina (Figure 1) [10, 32-34]. However, greyscale IVUS cannot reliably assess either the lipid content or the necrotic core of a plaque even using sophisticated image densitometric analysis [35].

Extensive calcification is uncommon in most IVUS studies of unstable lesions [10, 32-34]. Similarly, in one necropsy series of patients after sudden coronary deaths, over 50% of thin-cap atheromas showed either no calcium or only speckled calcium while 65% of actual ruptures demonstrated speckled calcium [4]. Finally, *in vitro* biomechanical models have shown that in contrast to lipid pools which dramatically increase fibrous cap stresses, calcium does not seem to affect the mechanical stability of the atheroma although it does appear that mildly to moderately calcified plaques are the ones most prone to rupture [5, 36]. Recently IVUS analyses have suggested that spotty calcification – multiple, small-sized calcium deposits – is more common in acute myocardial infarction lesions

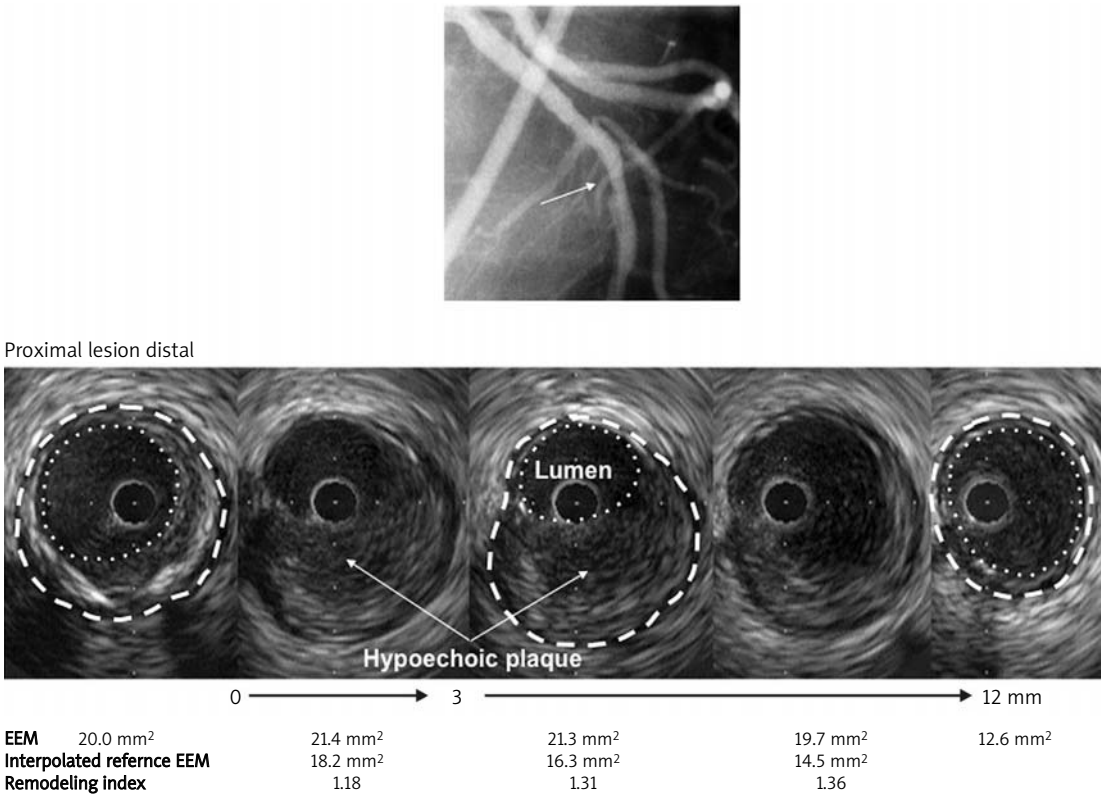

Figure 1. This patient presented with an acute coronary syndrome and a culprit lesion in the LAD (white arrow in the angiogram). The IVUS pullback shows the distal reference, three lesion cross-sections, and the proximal reference. The lumen is indicated by the inner dotted white line, and the EEM is indicated by the outer dashed white line, and the remodeling index is calculated as lesion EEM divided by reference EEM. Several approaches can be used to assess remodeling. The lesion EEM can be divided by the average of the proximal and distal reference EEM, an interpolated reference can be calculated (as shown), or the lesion can be compared to the proximal reference. Regardless of the approach, this patient has positive remodeling. Despite only modest lumen compromise, there is a large plaque burden (75%) at the lesion site. A large plaque burden should not be misinterpreted as representing a significant stenosis because the EEM grows to accommodate plaque accumulation and preserve lumen dimensions; in this example, the area stenosis (equivalent to the angiographic diameter stenosis) only measured 39%. In addition, there is a large area of superficial, eccentric, hypoechoic plaque (plaque that is less dense than the reference adventitia) (from Mintz GS. Intracoronary Ultrasound. London, Taylor and Francis Group, 2005)

[37, 38]. Radiofrequency IVUS analysis suggests that these small calcium deposits may be evidence of previous plaque rupture (the necrotic core "dumps" calcium).

There is, therefore, a paradox. Electron-beam computed tomographic (EBCT) studies have shown that the magnitude of coronary calcium is predictive of coronary events [39, 40]. If IVUS studies show that calcium is not related to plaque instability and that calcium is less common or less dense in plaques associated with ACS, what is the explanation for the predictive value of EBCT coronary calcium and subsequent events? Both pathologic and IVUS studies have shown that coronary calcium rarely occurs in the absence of coronary atherosclerosis and that overall plaque burden is roughly proportional to the amount of calcium [41-43]. Total arterial plaque burden is an important determinant of events and patient outcomes [1, 2]; presumably, a greater plaque burden increases the probability that an unstable lesion will develop.

Recent studies have focused on attenuated plaque – hypoechoic plaque with deep ultrasound attenuation – in patients with ACS (Figure 2). In an as yet unpublished study (Lee S-Y, personal communication) attenuated plaque was observed in 39.6% of STEMI vs. 17.6% of non-STEMI, but in no patients with stable angina. In ACS patients with attenuated plaques (1) the level of c-reactive protein (CRP) was higher; (2) angiographic thrombus and initial coronary flow < TIMI 2 were more common; and (3) and IVUS thrombus, positive remodeling, and plaque rupture were more common. Attenuated plaque appears to contain thrombus and microcalcification and to be associated with an increased risk of distal embolization post-intervention [44].

Finally, while the diagnosis of thrombus by IVUS must be considered presumptive [9], many studies have also reported more IVUS-evident thrombus in ACS lesions [45, 46] ACS patients who are troponin (+) have more evidence of thrombus than ACS patients who are troponin (–) [47]. The association of thrombus and clinical instability in patients with ruptured plaques has also been reported by Maehara *et al*. [23].

Plaque rupture

Intravascular ultrasound features of a ruptured plaque are consistent with histology – a cavity that communicated with the lumen with an overlying residual fibrous cap fragment (Figure 3) [22, 23, 48-51]. The highest rates of IVUS-detected plaque ruptures in ACS patients approach the frequency found on autopsy. It is unclear why the post-rupture fibrous cap remnant is easier to see than the fibrotic cap pre-rupture. Possibilities include (1) the remnant is thicker than pre-rupture similar to a rubber band that has been stretched and then released, (2) plaque and thrombus components adhere to the remnant increasing its thickness and echogenecity, and (3) the remnant is surrounded by blood and not other plaque components unless the cavity fills with thrombus to create limitations similar to pre-rupture.

In one large series of 300 IVUS plaque ruptures in 257 arteries in 254 patients, approximately two-third of fibrous caps ruptures were at the lateral attachment to the vessel wall, and one-third rupture

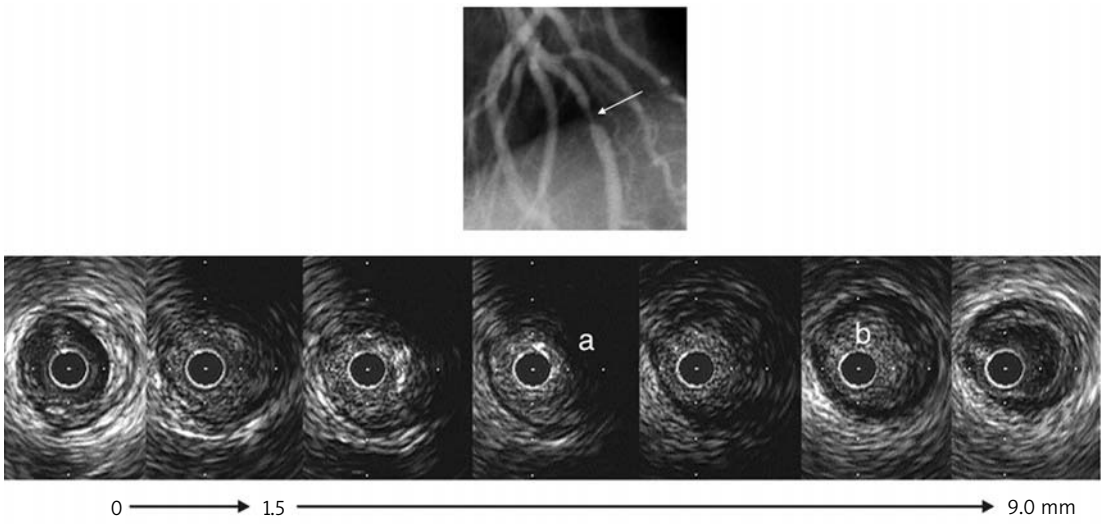

Figure 2. This patient presented with an evolving ST-elevation anterior myocardial infarction (white arrow in the angiogram). The IVUS study showed speckled plaque with attenuation ("a") obliterating the lumen, but without the classical features of plaque rupture or thrombus formation. Note the blood stasis ("b") distal to the occlusive lesion (from Mintz GS. Intracoronary Ultrasound. London, Taylor and Francis Group, 2005)

in the middle of the fibrotic cap [23]. Rupture in the middle of the fibrous cap requires significantly more stress compared to rupture at the lateral attachment to the vessel wall. Almost all angiographic complex lesions – either ulceration, intimal flap, lumen irregularity, thrombus, and aneurysm – are associated with IVUS ruptured plaques validating the commonly used Ambrose angiographic identification of ACS lesions [23, 52, 53]. However, the converse is not true; and angiography can miss plaque ruptures especially multiple discrete plaque ruptures in the same artery.

Von Birgelen *et al*. showed that the size of the ruptured plaque cavity was larger in lesions with positive remodeling and had a linear relation with lesion plaque and EEM size and with the reference dimensions, but not with the degree of lumen narrowing [54]. Unlike IVUS, histopathologic necropsy study rarely shows a distinct cavity (Virmani R, personal communication). *In vivo* coronary flow may displace the flap into the lumen (IVUS), or in vitro the flap may be displaced toward the residual plaque (histology).

Culprit and non-culprit ruptured plaques

Intravascular ultrasound studies have reported culprit lesion ruptured plaques in a varying percentage of ACS patients that seems to average slightly less than 50% [51, 55-57]. Rioufol *et al*. reported a series of 24 acute coronary syndrome patients with three-vessel IVUS imaging [51]. In this report there were 50 ruptured plaques: 9 (37.5%) within the culprit lesion and 41 at nonculprit sites including 16 patients with ruptures in two arteries and 3 patients with ruptures in all three arteries. Thus, surprisingly, most of the ruptured plaques were at sites remote from the culprit lesion; and 79% of patients had a secondary (remote) plaque rupture. However, these findings have not been confirmed by other investigators. For example, Hong *et al*. studied all three major epicardial arteries in 235 patients: 122 during acute infarct intervention and 113 in patients with stable angina. Primary plaque ruptures were present in 80 infarct patients (66%) and in 31 stable angina patients (27%); secondary (non-infarct-related or non-target artery) plaque ruptures were seen in 21 patients with acute myocardial infarction (17%) and in 6 patients with stable angina (5%) [57]. Studies by Tanaka *et al*. and Sumitsuji *et al*. were more in keeping with the report by Hong than the report by Rioufol [58, 59].

There are several possible reasons for the varying frequency of primary and secondary plaque ruptures among these different studies: (1) errors in identifying the culprit site; (2) the presence of thrombi that obscured the ruptured plaque cavity and the fibrous cap remnant; (3) the limited sensitivity of IVUS in detecting plaque rupture, especially small plaque ruptures; (4) lesions responsible for symptomatic ACS may not contain ruptured plaques, but merely large, bulky, hypoechoic plaques or erosive morphology; (5) some fibrous cap remnants may be below the threshold of IVUS resolution or lie too close to the transducer; and/or (6) some plaque ruptures may have an atypical IVUS appearance. However, there does

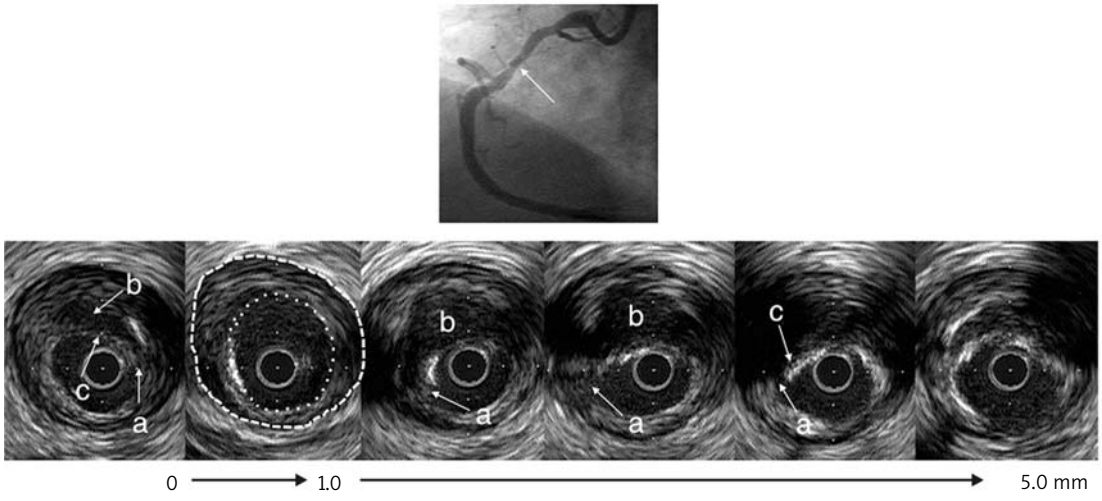

Figure 3. This is an example in which two tears occurred within the same fibrous cap, both at the junction of the fibrous cap and vessel wall. The lesion is shown by the white arrow in the angiogram. The IVUS image shows the two lateral tears in the fibrous cap ("a"), the evacuated cavities ("b"), and the residual fibrous cap fragments ("c"). The two tears are separated by a short segment of artery with an intact fibrous cap where, as in Figure 1, the EEM is indicated by the outer dashed line and the lumen by the inner dotted line (from Mintz GS. Intracoronary Ultrasound. London, Taylor and Francis Group, 2005)

appear to be an association between ACS and multiple plaque ruptures (regardless of the frequency) and between CRP and plaque rupture in ACS patients [56-58].

Symptomatic versus asymptomatic ruptured plaques

Not all ruptured plaques are associated with acute events [23]. Furthermore, secondary, nonculprit plaque ruptures are, by definition, asymptomatic; and there is now serial IVUS evidence that nonculprit ruptured plaques can heal or progress to form a stenosis without causing an acute event [60, 61] supporting the hypothesis that plaque rupture may be one of the mechanisms of stenosis progression, even in the absence of an acute event [62-65].

Fujii *et al*. compared the morphology of culprit ruptured plaques in ACS patients with "incidental" ruptured plaques [46]. Multivariate analysis identified smaller minimum lumen area and presence of thrombus as independent predictors of plaque ruptures that caused ACS events (Figure 4). This suggested that plaque rupture, itself, did not lead to symptoms. Instead, it was the association of plaque rupture with a smaller lumen area and/or lumen-compromising thrombus formation that led to acute symptoms. However, Maehara *et al*. showed that the minimum lumen area was usually not at the rupture site, but proximal to the minimum lumen site in 47% and distal to the minimum lumen site in 27% [23].

Most lesions causing an acute event arise from previous angiographically mild stenoses. This has lead to the misconception that vulnerable plaques are insignificant plaques. Fujii *et al*. used IVUS to study 112 ruptured plaques to create a pre-rupture "profile" of vulnerable plaques [66]. The narrowest coefficient of variance were for lesion EEM area, maximum plaque thickness, and plaque burden; reference lumen area; and remodeling index; conversely, there was a great variability in measures of calcification and lumen compromise (minimum lumen area and area stenosis). Thus, symptomatic

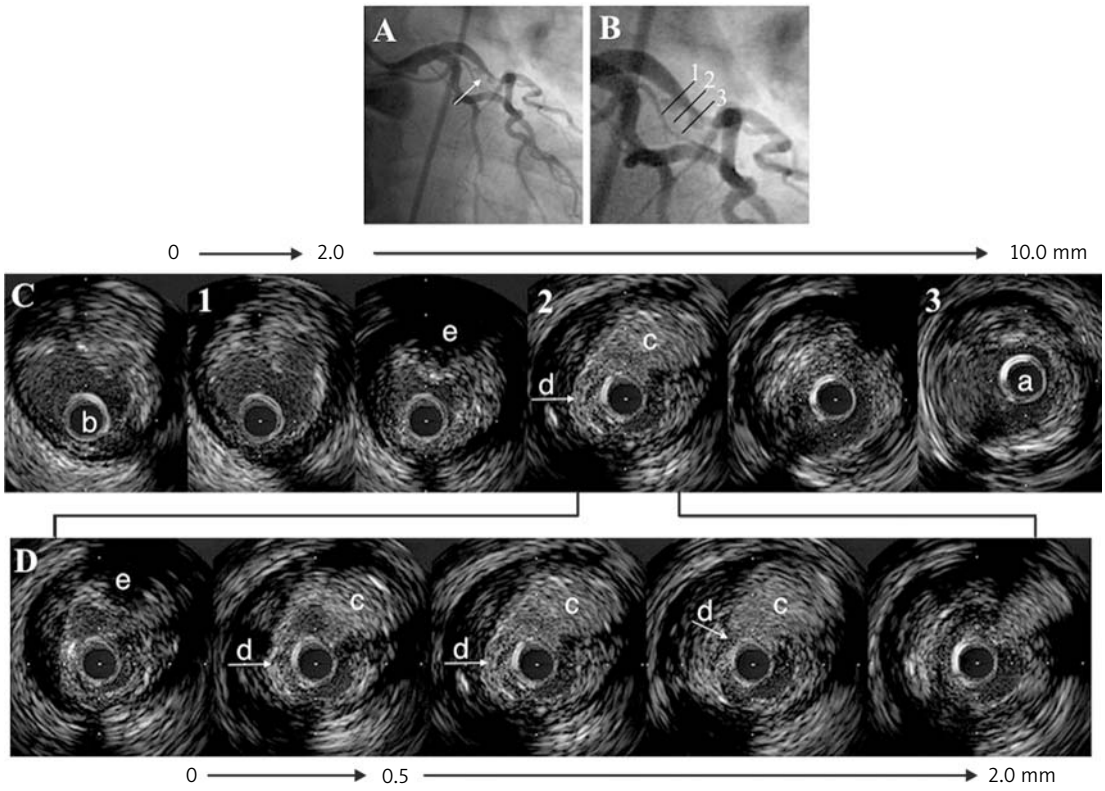

Figure 4. This patient presented with a non-Q myocardial infarction and a complex plaque in the left anterior descending artery (white arrows in Panel A). Two IVUS imaging runs from distal ("a") to proximal ("b") are shown; in Panel C the image slices are 2.0mm apart, and in Panel D the slices are 0.5mm apart allowing greater detail to be shown. Note the thrombus that originates in the ruptured plaque cavity ("c") and that protrudes into where it wraps around the IVUS catheter the lumen ("d") to encroach on the lumen. In some frames ("e") the thrombus is associated with attenuation. The lines in Panel B correspond to the IVUS image slices "1" through "3." When the angiogram is reviewed with the IVUS information in mind, there is a thrombus ("2") within a ruptured plaque cavity ("1" and "3") (from Mintz GS. Intracoronary Ultrasound. London, Taylor and Francis Group, 2005)

plaque ruptures did not occur at minimal disease sites. Rather, vulnerable (rupture-prone) plaques predictably had significant plaque accumulation and remodeling and occurred in larger arteries. It was only the degree of lumen compromise that was variable. Furthermore, both angiographic and IVUS studies have shown that the likelihood that any one lesion will lead to an event is related to its baseline stenosis severity [67-69]. This is nicely explained by the following statement from Kern and Meier: "Because the aggregate risk of rupture associated with many non-significant lesions (each with an admittedly lower individual risk potential) exceeds that of the fewer significant lesions, a myocardial infarction will more likely originate from a nonsignificant lesion" [70]. Thus, lumen dimensions should not be ignored in assessing unstable lesions; and chronically stenotic plaques with severe calcification, old thrombus, and eccentric lumens are included in the list of vulnerable plaque types [1, 2].

Ruptured plaque location

Hong *et al.* reported the location of culprit and secondary plaque ruptures in 392 patients, 231 with ACS and 161 with stable angina [71]. The distance between each coronary plaque rupture segment and the respective coronary ostium was measured with motorized IVUS transducer pullback. Overall, 83% of LAD plaque ruptures were predominantly located between 10 and 40 mm from the LAD ostium, LCX plaque ruptures were evenly distributed in the entire LCX tree, and 48% of RCA plaque ruptures were located between 10 and 40 mm from the RCA ostium and another 32% were located >70 mm from the ostium (Figure 5). Wang *et al*. reported the angiographic location of acute epicrdial thrombosis in 208 patients with STEMI [72]; occlusions tended to cluster within the proximal third of each of the vessels: LAD, LCX, and RCA. The difference between the angiographic study of Wang *et al*. and the IVUS study of Hong *et al*. was attributed to the paucity of sidebranches in the RCA leading to retrograde propagation of post-rupture thrombosis so that the site of acute angiographic occlusion in the RCA was often proximal to the more-distal site of plaque rupture.

Predicting vulnerable plaques

As mentioned at the beginning of this review, only one study has attempted to use greyscale IVUS to predict plaque instability. Yamagishi *et al*. retrospectively examined 114 coronary sites in 106 patients

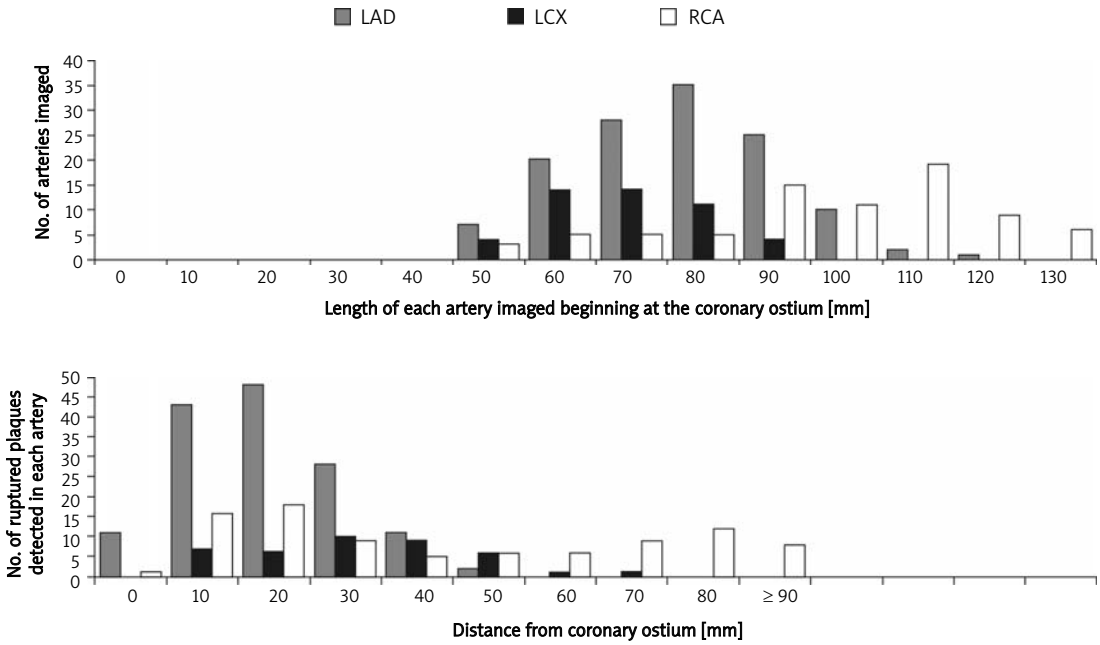

Figure 5. Hong *et al*. [71] performed three-vessel IVUS examination in 392 patients; 231 had ACS and 161 had stable angina pectoris. IVUS detected plaque ruptures in 206 patients: 158 ACS patients and 48 SAP patients. Multiple plaque ruptures (≥ 2 plaque ruptures) were observed in 53 patients (40 ACS and 13 stable angina patients). Thus, a total of 273 plaque ruptures were detected in 247 coronary arteries: 143 ruptures in 128 LADs, 40 ruptures in 38 LCXs, and 90 ruptures in 81 RCAs. The length of coronary artery imaged by IVUS was 83 ±14 mm in the LAD, 77 ±12 mm in the LCX, and 101 ±22 mm in the RCA. The distance between each plaque rupture segment and the respective coronary ostium was measured with motorized IVUS transducer pullback. The frequency of plaque ruptures located in segments 0-30 mm, 30-60 mm, 60-90 mm, and > 90 mm from the coronary ostium *when these corresponding segments were actually imaged* (thereby, excluding segments that could not be reached with the IVUS catheter) were 61% (150/247), 35% (86/247), 13% (29/233), and 8% (8/102)

without significant stenosis by angiography (< 50% diameter stenosis) [6]. During the follow-up period of 21.8 ±6.4 months, 12 patients had an acute coronary event at a previously examined coronary plaque. These pre-existing plaques were eccentric with a plaque burden of 67 ±9% and a lumen area of 6.7 ±3.0 mm^2, and eight of them had a shallow hypoechoic area. While the many IVUS studies of unstable and/or ruptured plaques and patients with ACS have shown the consistent results summarized above, no one has reproduced these prospective observations.

Recent radiofrequency-based, IVUS-derived technologies such as palpography and virtual histology are being studied for their potential to predict individual lesion plaque rupture. The PROSPECT Trial enrolled 700 patients with an ACS event, and three-vessel IVUS imaging was performed after treatment of the culprit lesion in order to relate baseline imaging – angiography, IVUS, and the new radiofrequency-IVUS derived technologies of palpography and virtual histology – to late events in an attempt to predict patients and lesions at risk for subsequent ACS.

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