# Angioscopic and Virtual Histology Intravascular Ultrasound Characteristics of Culprit Lesion Morphology Underlying Coronary Artery Thrombosis

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**Although rupture of vulnerable plaque with subsequent thrombosis is the most common mechanism of acute coronary syndromes, a significant percentage of patients with acute coronary syndrome may not have plaque rupture. We used angioscopy and virtual histology intravascular ultrasound (VH-IVUS) to investigate the underlying morphology of coronary thrombosis. We correlated the angioscopic diagnosis of coronary thrombosis in 42 lesions (37 patients) with gray-scale and VH-IVUS findings of the underlying plaque. By angioscopy plaque rupture was present in 19 thrombotic lesions (45.2%), whereas 23 (54.8%) had no rupture. VH-IVUS findings comparing thrombotic lesions with to those without angioscopic plaque rupture were remarkably similar except that angioscopic nonruptures tended to have more necrotic core (NC) at the minimum lumen area site (22.2 ± 12.5% vs 16.3 ± 9.3%, p = 0.09) and at the maximum NC site (32.7 ± 12.8% vs 25.0 ± 12.1%, p = 0.053) compared to angioscopic ruptures. Furthermore, among 19 lesions with angioscopic plaque rupture, there were 11 VH thin-cap fibroatheromas (TCFAs; 57.9%); among 23 lesions without angioscopic rupture, there were 17 VH-TCFAs (73.9%, p = 0.22). In conclusion, the similarity of VH-IVUS plaque composition (percentage of NC and percentage of VH-TCFA) in lesions with or without angioscopic plaque rupture suggest a spectrum of underlying morphologies to explain thrombosis in the absence of a ruptured plaque including classic erosions, small (and undetectable) plaque ruptures, and potentially unruptured TCFAs with superimposed thrombosis.**  **(Am J Cardiol 2011;107:1285–1290)**

Pathologic studies have demonstrated that most acute coronary syndromes occur from coronary thrombosis caused by rupture of a thin fibrous cap or surface erosion in the absence of cap disruption. Thin-cap fibroatheroma (TCFA) is currently regarded the main type of rupture-prone and thrombosis-prone vulnerable plaque.[1–7] Similar studies with angioscopy have revealed disruption of lipid-rich yellow plaques and subsequent thrombosis.[8–11] Yellow color intensity as evaluated by angioscopy is determined by thickness of the fibrous cap and is associated with plaque vulnerability.[12,13] Gray-scale intravascular ultrasound (IVUS) imaging is limited with regard to analysis of plaque composition. Virtual histology (VH) IVUS was developed to assess plaque composition. VH-IVUS characterizes plaque as fibrous tissue, fibrofatty plaque, dense calcium, and necrotic core (NC).[14] Although pathologic analysis of material retrieved by thrombectomy is enlightening, there are still limited in vivo data regarding coronary thrombus in relation to underlying plaque morphology. The aim of the present study was to investigate the underlying morphology of coronary thrombosis using VH-IVUS and angioscopy.

## Methods

From January 2006 through May 2008, 37 patients presenting with various manifestations of coronary artery disease, but mostly with acute coronary syndromes (33 of 37, 89%) were included in the present study. All patients had ≥1 angiographically visible thrombotic lesion in the culprit vessel, but some patients had >1 lesion with thrombus in the culprit vessel. Angiographic definition of coronary thrombus was the presence of a filling defect.[15] All primary and secondary thrombotic lesions were then divided into 2 groups according to whether there was an angioscopically defined ruptured plaque. These lesions were matched to gray-scale and VH-IVUS studies using angiographic landmarks. Informed consent was obtained from all patients. The protocol was approved by the Osaka Police Hospital ethical committee.

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Table 1
Baseline patient characteristics

| Variable | Overall (n = 37) | Nonrupture (n = 19) | Rupture (n = 18) | p Value |
|---|---|---|---|---|
| Age (years) | 60 ± 12 | 57 ± 11 | 61 ± 12 | 0.29 |
| Men | 30 (81%) | 12 (63%) | 18 (100%) | 0.004 |
| Women | 7 (19%) | 7 (37%) | 0 (0%) | |
| Risk factors | | | | |
| Hyperlipidemia | 30 (81%) | 17 (90%) | 13 (72%) | 0.35 |
| Hypertension | 25 (68%) | 13 (68%) | 12 (67%) | 0.54 |
| Diabetes mellitus | 12 (32%) | 8 (42%) | 4 (24%) | 0.41 |
| Current smokers | 15 (41%) | 8 (42%) | 7 (39%) | >0.99 |
| Clinical syndrome | | | | 0.65 |
| Acute myocardial infarction | 24 (60%) | 14 (74%) | 10 (56%) | |
| Unstable angina pectoris | 9 (30%) | 3 (16%) | 6 (33%) | |
| Stable angina pectoris | 2 (5%) | 1 (5%) | 1 (6%) | |
| Silent ischemia | 2 (5%) | 1 (55%) | 1 (6%) | |
| Target coronary vessel | | | | 0.08 |
| Left anterior descending | 16 (43%) | 10 (53%) | 6 (33%) | |
| Right | 14 (38%) | 4 (21%) | 10 (56%) | |
| Left circumflex | 7 (19%) | 5 (26%) | 2 (11%) | |
| Lesion distribution | | | | 0.16 |
| Patients with 1 lesion | 32 (87%) | 15 (79%) | 17 (94%) | |
| Patients with 2 lesions | 5 (14%) | 4 (21%) | 1 (6%) | |

Lipid disorder was defined as total cholesterol level ≥200 mg/dl, low-density lipoprotein cholesterol ≥100 mg/dl, high-density lipoprotein cholesterol <50 mg/dl, triglycerides ≥150 mg/dl, or medication use. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of an antihypertensive drug. Patients with diabetes mellitus had a confirmed diagnosis or were under antidiabetic treatment at the time of their study.

Catheterization was performed by the radial, brachial, or femoral approach using 6Fr or 7Fr sheaths and catheters. Intravenous heparin (100 U/kg) was administered at the beginning of catheterization. The culprit vessel was examined first by angioscopy and then by IVUS. Of the 37 examined patients 12 had aspiration thrombectomy and 6 had balloon predilation before IVUS or angioscopy was performed.

Angioscopy was performed only in patients with angiographically visible coronary thrombus. Angioscopic observation was performed from the distal segment to the ostium of the vessel before and, if necessary, after percutaneous coronary intervention to study the entire target vessel. An angioscope (RX-3310A and MV-5010A, Machida, Tokyo, Japan) and optic fiber (DAG-2218LN, Machida) were used. Angioscopic observations were made while blood was cleared from view by an injection of 3% dextran-40 as previously reported.[10] Angioscopic images were viewed in real time on a monitor and afterward from recordable compact disks.

A phased-array, 20-MHz, 3.2Fr IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, California) was placed into the distal coronary artery after intracoronary administration of nitroglycerin 0.2 mg and was pulled back manually to the aorto-ostial junction. During pullback, gray-scale IVUS was recorded, raw radiofrequency data were captured at the top of the R wave, and reconstruction of the color-coded map by a VH-IVUS data recorder was performed (In-Vision Gold and S5, Volcano Corporation). Gray-scale IVUS and captured radiofrequency data were copied to a recordable digital video disk for off-line analysis.

Thrombus-containing lesions were classified as having plaque rupture or, in the absence of criteria for plaque rupture, nonrupture.[16,17] Angioscopically, plaque rupture required ≥2 of the following criteria: (1) >50% of luminal area occupied by thrombus or protruded plaque content, (2) presence of a large cavity or fissure, (3) thrombus over yellow plaque, and (4) distal embolism observed by angioscopy.

Yellow plaque was defined as a yellow area on the luminal surface with a smooth or irregular surface with or without protrusion into the lumen.[11,13] Number of yellow plaques in the culprit artery and yellow color intensity of each of those plaques were also evaluated. Yellow color was graded as 1 (light yellow), 2 (yellow), or 3 (intense yellow) as previously reported.[11,13] If a thrombus-containing lesion had multiple yellow color grade values, the highest score was reported.

Angioscopic images were interpreted by 2 angioscopic specialists (Y.U. and T.K.); disagreement was settled by a third reviewer. There were no cases in which each of the 3 reviewers judged different color grades; in all cases ≥2 reviewers agreed on color classification.

Off-line gray-scale and VH-IVUS analyses were performed using pcVH 2.1 and VIAS 3.0 (Volcano Corporation). Gray-scale IVUS measurements of lumen, external elastic membrane (EEM), and plaque and media (defined as EEM minus lumen) cross-sectional areas and plaque burden (defined as plaque and media divided by EEM) were performed for every recorded frame. Remodeling index was calculated as lesion EEM divided by mean reference EEM.[18] VH-IVUS analysis was also performed for every recorded frame. The 4 VH-IVUS plaque components were reported as percent plaque area.[19] Lesions were classified by 2 experienced independent observers (E.S. and A.M.) based on plaque composition according to previous published definitions[20]: pathologic intimal thickening, VH-IVUS–derived TCFA (VH-TCFA), thick-cap fibro-

Table 2
Angioscopic data

| Variable | Overall (n = 42) | Nonrupture (n = 23) | Rupture (n = 19) | p Value |
|---|---|---|---|---|
| Number of yellow plaques | 1.9 ± 1.4 | 1.5 ± 1.2 | 2.5 ± 1.4 | 0.01 |
| Grade | | | | 0.001 |
| 3 | 30 (71%) | 11 (48%) | 19 (100%) | |
| 2 | 10 (24%) | 10 (44%) | 0 (0%) | |
| 1 | 2 (5%) | 2 (9%) | 0 (0%) | |
| Thrombus | | | | <0.00001 |
| Mixed (red/white thrombus) | 22 (52%) | 3 (13%) | 19 (100%) | |
| Red thrombus | 14 (33%) | 14 (61%) | 0 (0%) | |
| White thrombus | 6 (14%) | 6 (26%) | 0 (0%) | |

Table 3
Virtual histologic intravascular ultrasound data

| Variable | Overall (n = 42) | Nonrupture (n = 23) | Rupture (n = 19) | p Value |
|---|---|---|---|---|
| Virtual histologic lesion phenotype | | | | 0.53 |
| Thin-cap fibroatheroma | 28 (66%) | 17 (74%) | 11 (58%) | |
| Thick-cap fibroatheroma | 12 (29%) | 5 (22%) | 7 (37%) | |
| Pathologic intimal thickening | 2 (5%) | 1 (4%) | 1 (5%) | |
| Proximal reference site | | | | |
| External elastic membrane area ($mm^2$) | 19.0 ± 6.8 | 16.8 ± 4.8 | 21.6 ± 8 | 0.02 |
| Lumen area ($mm^2$) | 7.0 ± 2.8 | 6.5 ± 2.0 | 7.6 ± 3.4 | 0.25 |
| Plaque burden (%) | 61.1 ± 10.8 | 59.6 ± 9.3 | 62.9 ± 12.3 | 0.34 |
| Distal reference site | | | | |
| External elastic membrane area ($mm^2$) | 15.0 ± 5.1 | 13.6 ± 4.7 | 16.5 ± 5.3 | 0.06 |
| Lumen area ($mm^2$) | 5.2 ± 1.8 | 4.7 ± 1.9 | 5.7 ± 1.7 | 0.11 |
| Plaque burden (%) | 63.9 ± 8.5 | 63.1 ± 9.6 | 64.8 ± 7.1 | 0.52 |
| Minimum lumen area site | | | | |
| External elastic membrane area ($mm^2$) | 17.7 ± 5.3 | 15.7 ± 4.1 | 20.1 ± 5.6 | 0.005 |
| Lumen area ($mm^2$) | 3.3 ± 1.1 | 3.2 ± 1.1 | 3.5 ± 1.2 | 0.48 |
| Plaque and media area ($mm^2$) | 14.3 ± 4.9 | 12.4 ± 3.6 | 16.6 ± 5.4 | 0.04 |
| Plaque burden (%) | 80.1 ± 6.2 | 78.7 ± 5.7 | 81.8 ± 6.6 | 0.11 |
| Necrotic core (%) | 19.6 ± 11.4 | 22.2 ± 12.5 | 16.3 ± 9.3 | 0.09 |
| Dense calcium (%) | 6.4 ± 4.9 | 7.6 ± 5.2 | 5.0 ± 4.2 | 0.08 |
| Fibrofatty (%) | 12.6 ± 7.7 | 12.2 ± 7.9 | 13.0 ± 7.6 | 0.75 |
| Fibrotic (%) | 53.3 ± 9.7 | 53.4 ± 8.5 | 53.3 ± 11.1 | 0.96 |
| Remodeling index | 1.2 ± 0.5 | 1.12 ± 0.4 | 1.24 ± 0.5 | 0.42 |
| Maximum necrotic core site | | | | |
| External elastic membrane area ($mm^2$) | 17.2 ± 4.8 | 16.0 ± 4.4 | 18.6 ± 5.0 | 0.07 |
| Lumen area ($mm^2$) | 4.9 ± 1.7 | 4.7 ± 1.6 | 5.2 ± 1.7 | 0.29 |
| Plaque and media area ($mm^2$) | 12.2 ± 4.3 | 11.3 ± 3.6 | 13.4 ± 4.8 | 0.11 |
| Plaque burden (%) | 70.3 ± 8.2 | 69.9 ± 7.7 | 70.8 ± 8.9 | 0.73 |
| Necrotic core (%) | 29.2 ± 12.7 | 32.7 ± 12.8 | 25.0 ± 12.1 | 0.053 |
| Dense calcium (%) | 9.9 ± 7.0 | 11.2 ± 8.3 | 9.2 ± 4.7 | 0.17 |
| Fibrofatty (%) | 6.8 ± 6.6 | 6.0 ± 4.8 | 7.6 ± 6.3 | 0.43 |
| Fibrotic (%) | 45.0 ± 12.7 | 45.5 ± 12.1 | 44.4 ± 9.3 | 0.73 |
| Remodeling index | 1.1 ± 0.4 | 1.12 ± 0.4 | 1.14 ± 0.4 | 0.91 |

atheroma (ThCFA), fibrotic plaque, and fibrocalcific plaque. In particular, VH-TCFA was a fibroatheroma without evidence of a fibrous cap: >10% confluent NC with >30° NC abutting the lumen in ≥3 consecutive frames. ThCFA was a fibroatheroma (>10% of confluent NC in ≥3 consecutive frames) with a definable fibrous cap.

Statistical analysis was performed with StatView 5.0 (SAS Institute, Cary, North Carolina). Continuous variables were presented using mean ± SD. Categorical variables were summarized as absolute value and percentage. Continuous variables were tested for normal distribution by nonparametric 1-sample Kolmogorov–Smirnov test; all showed normal distribution and were compared using unpaired Student's *t* test. Categorical variables were compared to chi-square or Fisher's exact test. A p value <0.05 was considered statistically significant.

## Results

Baseline patient characteristics are listed in Table 1. Acute myocardial infarction was present in most patients (24 of 37, 59.5%) with ST-elevation myocardial infarction

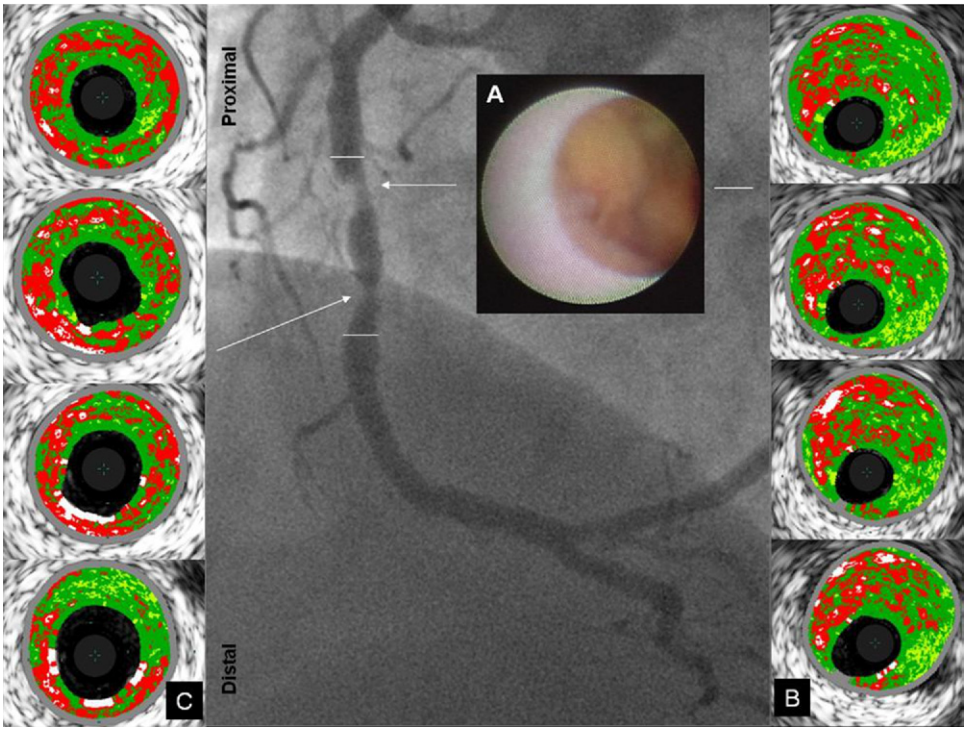


Figure 1. Mid right coronary artery lesion with plaque rupture and thrombus. *(A)* Angioscopic high-grade yellow plaque with rupture covered by "red/white" thrombus. *(B)* Consecutive frames of virtual histology intravascular ultrasound analysis show high percentage of plaque burden and necrotic core—classified as thick-cap fibroatheromas. *(C)* Consecutive frames of virtual histology intravascular ultrasound analysis show high percentage of plaque burden and necrotic core—classified as thin-cap fibroatheromas.

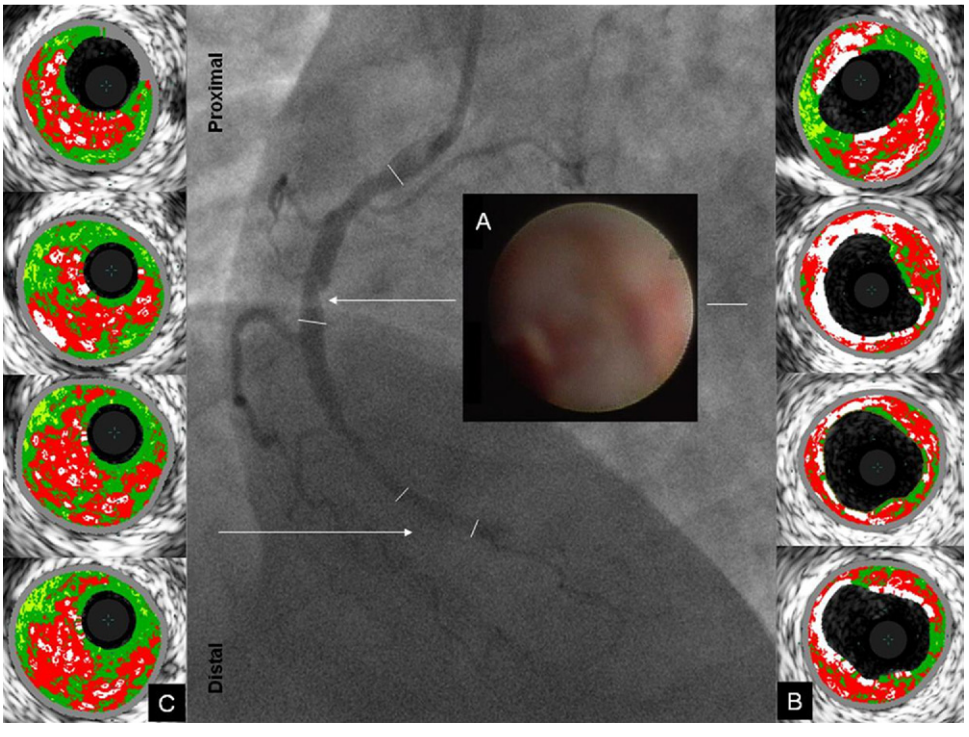


Figure 2. Distal and mid right coronary artery lesions with thrombus in absence of plaque rupture. *(A)* Angioscopic yellow plaque without rupture covered by "red" thrombus. *(B)* Consecutive frames of virtual histology intravascular ultrasound analysis show high percentage of plaque burden and necrotic core—classified as thin-cap fibroatheromas. *(C)* Consecutive frames of virtual histology intravascular ultrasound analysis show high percentage of plaque burden and necrotic core—classified as thin-cap fibroatheromas.

in 14 patients. At time of catheterization, 5 of 37 patients (13.5%) had complete thrombotic occlusion.

Thirty-two patients had 1 thrombotic lesion and 5 patients had 2 thrombotic lesions. Patients with 2 thrombotic lesions had angioscopic rupture or no rupture, but never the 2 together. Overall, 18 patients had 1 angioscopic plaque rupture or 2 angioscopic plaque ruptures, whereas 19 did not have any angioscopic plaque rupture. Men had more lesions with plaque rupture than lesions without plaque rupture ($p = 0.004$); conversely, no woman had a plaque rupture. There were no other significant differences regarding age, risk factors, clinical syndrome, and treated coronary artery between the 2 groups.

Overall, there were 42 discrete lesions with angioscopic thrombus. Angioscopic plaque rupture was present in 19 thrombotic lesions (45.2%); conversely, 23 (54.8%) were classified as nonruptures. Angioscopic rupture was associated with more yellow plaques, more grade 3 yellow plaques, and more adherent red/white thrombus than lesions without angioscopic plaque rupture (Table 2).

Angioscopic ruptures occurred in larger vessels (larger EEM) than lesions without angioscopic plaque rupture. However, there were no other gray-scale IVUS differences between the 2 groups (Table 3).

Quantitative VH-IVUS findings were also similar between angioscopic ruptures and nonruptures with the notable exception of a larger maximum percent NC in the nonrupture group than in the rupture group (Table 3).

Among the 42 angioscopic thrombotic lesions analyzed by VH-IVUS, there were 28 TCFAs (66.7%), 12 ThCFAs (26.6%), and 2 pathologic intimal thickenings (4.7%). Among the 19 lesions with angioscopic plaque rupture, there were 11 VH-TCFAs (57.9%, Figure 1); among the 23 lesions without angioscopic rupture, there were 17 VH-TCFAs (73.9%, $p = 0.22$, vs angioscopic ruptures; Figure 2, Table 3).

## Discussion

Our findings demonstrated that coronary atherosclerotic plaques with angioscopic thrombus have very similar compositional characteristics as assessed with gray-scale and especially VH-IVUS regardless of whether the angioscopic images showed plaque rupture or absence of plaque rupture. Similarity of VH-IVUS plaque composition (percent NC and percent VH-TCFA) in lesions with or without angioscopic plaque rupture suggests a spectrum of underlying morphologies to explain thrombosis in the absence of a ruptured plaque including classic erosions, small (and undetectable) plaque ruptures, and potentially unruptured TCFAs with superimposed thrombosis. In particular, the present study suggests that a VH-TCFA can lead to thrombosis without plaque rupture, especially in women.

Pathologically, luminal thrombosis occurs from 3 different causes: most often from plaque rupture, then erosion, and rarely from calcified nodules. Formation of intraluminal thrombus after plaque rupture or erosion plays a central role in the clinical course of acute coronary syndrome. The cause and pathogenesis of initiating event(s) causing rupture or erosion are distinct regarding inflammation, remodeling, and growth rates of underlying plaque.[21] Plaque rupture is histologically defined as a lesion consisting of an NC with an overlying thin ruptured fibrous cap that leads to luminal thrombosis because of contact of platelets with a highly thrombogenic NC.[22] Plaque erosion shows a luminal thrombus with an underlying base rich in proteoglycans and smooth muscle cells with minimal inflammation. Pathologically, most erosion lesions are devoid of an NC; but when present, the core does not communicate with the lumen because of a thick fibrous cap.[22] In the present in vivo angioscopic/VH-IVUS study, even angioscopic plaques with thrombosis but without rupture had a high percent NC and were classified as VH-TCFAs in almost 75%.

Virmani et al[7] proposed TCFA as a specific lesion that is a precursor of plaque rupture. Subsequent studies have defined TCFA fibrous cap thickness as $<65$ $\mu$m[23] and have shown that nearly 75% of TCFAs have $>10\%$ of the plaque area occupied by a lipid-rich NC.[22] In addition, an angioscopic study showed that plaques with an intense yellow color (high grade) were closely correlated with VH-TCFA.[24] In the present study most yellow plaques had high color intensity (grade 3) especially in the rupture group. Moreover, most culprit lesions were classified as VH-TCFA (66.7%); and the percentage of VH-TCFAs was high regardless of whether a rupture was present (57.9%) or not present (73.9%).

Angioscopic "diagnoses" of rupture and erosion may be different from pathology. In part angioscopic diagnosis of erosion is one of exclusion—i.e., a thrombotic lesion without features of rupture—whereas a pathologic diagnosis has distinct features. Angioscopy may miss small ruptures or ruptures obscured by thrombus.

Pathologic evidence supporting the important role of erosion in myocardial infarction has been reported by Arbustini et al[25] who reported that erosions accounted for 25% of 291 autopsied in-hospital deaths from myocardial infarction. A high percentage of thrombus without plaque rupture was also described in patients with myocardial infarction in the present population (14 of 24, 58.3%).

Risk factors for erosion are poorly understood and are different from those of rupture. On average eroded plaques are more frequent in younger patients, especially in women; and there is less severe narrowing at sites of thrombosis. Plaque erosion accounts for $>80\%$ of thrombi occurring in women $<50$ years of age. Consistently plaque erosion is associated with smoking, especially in women.[22,26–28] In contrast, plaque ruptures are more frequently associated with white race and hypertension.[29,30] In the present study there were no differences in predisposing factors and clinical syndrome between the 2 groups. However, in our cohort that was entirely Asian, patients in the nonrupture group tended to be younger than those in the rupture group; furthermore, all women had thrombotic lesions without plaque rupture.

The present study has several limitations. A thin fibrous cap $<65$ $\mu$m is below the spatial resolution of VH-IVUS ($\approx 150$ $\mu$m); therefore, all fibroatheromas with a fibrous cap thickness $<150$ $\mu$m will appear as TCFAs. Several patients had aspiration thrombectomy or balloon angioplasty before angioscopy and IVUS because of severe luminal narrowing; this influenced the amount of thrombus and underlying plaque morphology, although predilation should not have masked the presence of

plaque rupture. Of 18 patients with angioscopically documented plaque rupture, only 2 had balloon predilation before imaging. In patients with 2 thrombotic lesions, the distance between lesions was >5 mm; nevertheless, these 2 may have been related. VH-IVUS classifies thrombus as "green" (fibrous tissue) or "light green" (fibrofatty plaque), decreasing the relative size of the NC and converting a VH-TCFA to a ThCFA. Angioscopy may have missed some small plaque ruptures. The performance of angioscopy first may have affected the underlying morphology when VH-IVUS was done second.


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