

Characterization of coronary plaques with combined use of intravascular ultrasound, virtual histology and optical coherence tomography

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Abstract

According to post-mortem studies, luminal thrombosis occurs from plaque rupture, erosion and calcified nodules. *In vivo* studies have found thin cap fibroatheroma (TCFA) as the main vulnerable lesion, prone to rupture. Few data about other *post-mortem* lesions have been reported *in vivo*. Our main objective is to characterize *in vivo* the coronary plaques with intravascular ultrasound-virtual

histology (IVUS-VH) and optical coherence tomography (OCT), in order to detect not only thin cap fibroatheroma (TCFA), but also other possible vulnerable lesions. The secondary objective is to correlate these findings with clinical and analytical data. Twenty-five patients (18 stable) submitted to coronary angiography were included in this pilot study. After angiography, the three vessels were studied (when possible) with IVUS-VH and OCT. Plaque characteristics were correlated with clinical and analytical data. Forty-six lesions were analyzed. IVUS-VH detected significant necrotic core in 15 (3 were definite TCFA). OCT detected TCFA in 10 lesions, erosion in 6, thrombus in 5 and calcified nodule in 8. Possible vulnerable lesion was found in 61% of stable and 57% of unstable patients. Erosions and calcified nodules were only found in stable patients. Those with significant necrotic core had higher body mass index ($P=0.016$), higher levels of hs-CRP ($P=0.019$) and triglycerides ($P=0.040$). The higher the levels of hs-CRP, the larger the size of the necrotic core ($r=0.69$, $P=0.003$). Lesions with characteristics of vulnerability were detected by IVUS-VH and OCT in more than 50% of stable and unstable coronary patients. A significant necrotic core was mainly correlated with higher hs-CRP.

authors have combined the three modalities^{10,11} due to technical difficulties. IVUS shows the amount of plaque and remodeling. VH constructs tissue maps that classify plaque into four major components: calcium, fibrous, fibrolipidic, and necrotic core (labeled white, green, greenish-yellow, and red, respectively).¹² However, VH does not allow us to measure cap thickness. With OCT we can measure cap thickness and visualize microstructures near the lumen, such as calcified nodules, erosions and small thrombi. The combination of VH plus OCT is needed to detect a definite "thin cap fibroatheroma" (TCFA).¹⁰ However, OCT-derived TCFA is usually accepted as TCFA.⁷

According to post-mortem studies by Virmani *et al.*,² luminal thrombosis occurs in 55-60% of patients with sudden cardiac death, erosion in 30-35% of cases and calcified nodule in 2-7%. The important point is to find intact lesions *in vivo* similar to those described as disrupted on pathological examination,¹³ in order to prevent the acute event.

The most studied precursor lesion for disrupted plaques is OCT-derived TCFA,⁷ although necrotic core,¹² erosions and calcified nodules could also be precursors.² In fact, some authors¹⁰ consider VH-derived TCFA as an abundant necrotic core (>10% of the cross-sectional area) in contact with the lumen and plaque-volume greater than 40%.

Erosions are the main cause of healing thrombi, with increased risk for distal intramyocardial embolization,¹⁴ therefore, small thrombi are thought to be indicative of erosion.^{2,15} Conventional imaging techniques, such as angiography or IVUS alone, are not sensitive enough to detect vulnerable plaques.⁴

The main objective of the present pilot study is to characterize the plaques of patients submitted to coronary angiography, trying to detect *in vivo* not only TCFA, but also other lesions possibly related to vulnerable and complicated plaques, with 3 different techniques: IVUS, VH and OCT. The secondary aim is to correlate these findings with clinical and analytical data.

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Introduction

In the last two decades many articles have been published with the term "vulnerable plaque". It is believed that vulnerable plaques are prone to rupture and therefore facilitate acute intracoronary thrombosis, with consequent acute coronary syndrome (ACS) and/or sudden death. Some reports are based on post-mortem studies¹² and others on different invasive and non-invasive techniques.^{3,4} Among invasive techniques, the most useful for this purpose are intravascular ultrasound (IVUS),⁵ IVUS-derived virtual histology (VH)⁶ and optical coherence tomography (OCT).^{7,9} Very few

Materials and Methods

Study design

Twenty-five consecutive patients (21 men), aged 62 ± 8 , scheduled for coronary angiography, were eligible for inclusion in a cross-sectional single-center pilot study. Eighteen patients had stable coronary disease (14 stable angina and 4 severe silent ischemia) and 7 had non-ST segment elevation ACS (4 with troponin elevation). All patients with stable disease had indication of coronary angiography due to refractory angina or a severely positive test for ischemia. Exclusion criteria were age (<18 and >80 years), significant renal dysfunction (creatinine clearance <50 mL/min) and prior coronary artery bypass or stent. Patients in whom only IVUS could be performed were also excluded.

Medical history, physical examination, electrocardiogram and general analyses (hemogram, biochemistry including hs-CRP) were performed. We assessed patient characteristics including age, sex, body mass index, and presence of cardiovascular risk factors: hypertension, hyperlipidemia, diabetes mellitus and smoking. Plasma creatinine was analyzed the day before and the day after the invasive procedure.

Prevention of contrast nephropathy was performed by means of acetyl cysteine 600 mg twice a day during the previous 48 hours plus oral hydration with 2 liters of water, one day before and after the invasive procedure, according to previous risk score.¹⁶

Diagnostic angiography was performed in all patients. Quantitative measurements were made with the commercial program QUANTCOR.QCA.3.0, Siemens (Munich, Germany). Luminal diameter stenosis of 70% or over was considered significant.

The study complied with the declaration of Helsinki. The locally appointed ethics committee approved the research protocol and written informed consent was obtained from the patients.

Imaging studies

Imaging of the 3 coronary arteries with IVUS-VH and OCT was attempted in every major artery after administration of 200 μ g of iv nitroglycerin. In case of severe calcification, very sinuous segments or chronic total occlusion, no attempt was made.

The order of performance was as follows: IVUS-VH in left anterior descending (LAD) and then in left circumflex (LCx) coronary artery; OCT in LAD and then in LCx artery; IVUS-VH followed by OCT in right coronary (RC) artery.

IVUS study was performed with commercially available catheters (2.9 F, 20-MHz, Eagle Eye,

Volcano Corporation, Rancho Cordova, USA). The catheter was advanced to the distal segment of the coronary arteries, guided by angiography and pulled back with an automatic device at a rate of 0.5 mm/sec to the aorto-coronary ostium. Data were analyzed with commercially available software (Volcano Corporation, Rancho Cordova, USA) according to standard validated criteria.¹⁷

VH is the radiofrequency data analysis of IVUS. It was performed with commercially available software (Volcano Corporation, Rancho Cordova, USA).

OCT was performed with "the Light Lab Imaging System" (Westford, Massachusetts, USA). An OCT 1.4-F catheter with occlusion balloon (Helios, Goodman Inc, Nagoya, Japan) was advanced distal to the lesion over a conventional coronary guide wire, which was then replaced by the OCT imaging catheter. The catheter was withdrawn with an automatic device at 1.0 mm/sec while the images were obtained. The occlusion balloon remained inflated at 0.4 atm near the coronary ostium. To visualize the entire coronary artery, the images were obtained in 3 pullbacks, using the bifurcations as references. In the last 8 patients, a continuous infusion of non-ionic radiological contrast (Visipaque[®]) at 0.5 ml/sec was used instead of the occlusion balloon to reduce the time of ischemia during imaging acquisition. With the new OCT software, the time of imaging acquisition was reduced, due to the automatic withdrawal speed at 3 mm/sec. This method was used in the last 5 patients.

The automatic progress of the catheter at a fixed speed with each technique made it possible to calculate with accuracy the exact location of the catheter in the artery, starting from a distal point. This point was marked by a conventional guide wire that remained in a fixed position while obtaining images with IVUS-VH and OCT. The exact location of the IVUS and OCT catheters was identified using different landmarks, such as side branches, angles of the vessel, and the tip of the guide wire.

The culprit plaques of unstable patients were not studied, to avoid any possible risk of distal emboli from a ruptured plaque. The remaining plaques of the coronary tree were studied after percutaneous treatment of the culprit lesion.

Imaging analysis

The images were analyzed separately by two interventional cardiologists according to established criteria.^{18,19} In case of discrepancy, a consensus between them was reached.

The borders of the external elastic membrane (EEM) and lumen were traced with IVUS. The enclosed area was defined as plaque area. The remodeling index was defined as the ratio

between the area inside the EEM of the lesion and the area inside the EEM of a reference site. The site with less atherosclerotic burden proximal to the lesion before any bifurcation was chosen as reference. A remodeling index greater than 1.05 was considered positive and less than 0.95 negative, whereas an index between 0.95 and 1.05 was no remodeling.²⁰

Tissue components were classified by VH as calcium, fibrous, fibrolipidic and necrotic core.¹³ Significant necrotic core was defined as a lesion fulfilling two criteria: necrotic core 10% or over in at least three consecutive frames and percentage of atheroma volume of 40 or over.¹³

Other measurements included length of the lesion, luminal volume and vessel volume. Plaque volume was calculated as vessel volume minus lumen volume. Percent atheroma volume was defined as $EEM_{area} - lumen_{area} \times 100$.¹⁷

An OCT image of a signal-poor lesion with unclear borders was diagnosed as lipid pool. When lipid was present in 2 or more quadrants in any of the images within a plaque it was considered to be a lipid-rich plaque.⁷ A signal-rich homogenous tissue overlying lipid content was called fibrous cap.^{7,10,18} Cap thickness for each image was measured 3 times and the average value was computed. OCT-derived TCFA was defined as a plaque with lipid content in 2 or more quadrants and the thinnest part of a fibrous cap measuring 65 μ m or under.⁷ In post-mortem studies,² TCFA has been defined as a plaque with a large necrotic core and a thin fibrous cap (<65 μ m). As IVUS-VH can detect the necrotic core and OCT the thin cap, both techniques are needed to detect a definite TCFA *in vivo*.¹⁰

Other lesions detected with OCT are plaque erosion, thrombi and calcified nodules. Plaque erosion was defined as loss of the endothelial lining with lacerations of the superficial intimal layers and with no *trans-cap* ruptures.²¹ It would be expected to find a thrombus attached to the erosion surface. However, the infusion of radiological contrast may displace the thrombus.

A thrombus was defined as an irregular mass 250 μ m or more protruding into the lumen, with apparently normal endothelial lining underneath.⁷

The calcified nodule has been defined as calcified plates along with bony nodules that penetrate the lumen.² We defined a calcified nodule at risk as one with a thin fibrous cap (<65 μ m).

Not only OCT-derived TCFA but also significant necrotic core, erosions, thrombi and calcified nodules were considered possible characteristics of vulnerability.

Statistical methods

The statistical analysis was performed using SPSS, version 15.0 (SPSS Inc., Chicago,

Illinois, USA). Data were expressed as mean \pm SD for continuous variables, and as percentages for categorical variables. Normality of variables was assessed with the Kolmogorov-Smirnov test. The Levene test was used to analyze homogeneity of the variance. Student's t-test and ANOVA were used for continuous variables and the χ^2 test for categorical variables. Pearson's correlation coefficient and Spearman's Rho were used to assess correlations between continuous variables.

Results

Table 1 shows the clinical and biochemical characteristics of the patients.

Imaging studies

Forty-six atherosclerotic plaques were studied in 31 different coronary arteries with at least one imaging technique (IVUS-VH or OCT). The intra- and inter-observer variation was less than 5%. Thirty-one (67%) lesions were studied with IVUS-VH plus OCT; 7 (15%) lesions were studied only with OCT and 8 (17%) only with IVUS-VH. Although attempts were made to perform all the imaging techniques in the 3 coronary arteries of every single patient, it was not always possible for different reasons: impossibility of catheter progression, long time of radiological exposure and difficulties analyzing some images for technical reasons. Figure 1 shows the percent of arteries studied with each imaging technique and Figure 2 the number of plaques with some characteristic of vulnerability in each patient. Forty-four percent of lesions were found in prox-

imal and middle segments of the anterior descending coronary artery.

As the correlation between OCT and IVUS-VH to detect TCFA is poor,¹⁰ we analyzed separately OCT-derived TCFA and necrotic core. Figure 3 shows the same plaque imaged with different imaging techniques (Figure 3).

Thirty-nine (85%) lesions were studied with IVUS-VH. Eighteen had positive remodeling, 13 negative and 8 no remodeling. NS difference in remodeling was detected between angiographically significant (n=26) and non-significant (n=13) lesions. Fifteen of the 39 (38%) lesions studied by IVUS-VH had a significant necrotic core with a variable degree of microcalcification inside (Figure 3C). Nine of 15 lesions with necrotic core were located in proximal and middle segments, while the 6 remaining lesions were found in distal coronary segments. Ten of the 15 lesions were angiographically significant. No correlation was found between the presence of significant necrotic core and positive remodeling or angiographic significance.

Thirty-eight (83%) lesions were studied with OCT. A TCFA was detected in 10 of them (Figures 3D, 4A and B). Six of 10 TCFA had positive remodeling, one negative and 3 no remodeling. Seven of 10 TCFA were found in proximal and middle segments of the LAD coronary artery. Five of 10 lesions with TCFA were angiographically significant. No correlation was found between the presence of TCFA and positive remodeling or angiographic significance. IVUS-VH could only be performed in 5 of the 10 OCT-derived TCFA. Three of them had necrotic core. Therefore, they were definite TCFA. Erosions were found in 6 lesions (2 with thrombi) (Figure 4D and F), all of them with negative remodeling

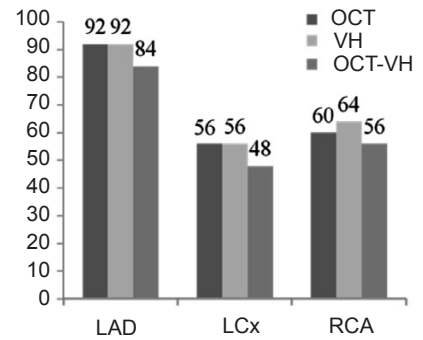


Figure 1. Percentage of arteries studied with each imaging technique. LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; OCT, optical coherence tomography; VH, virtual histology.

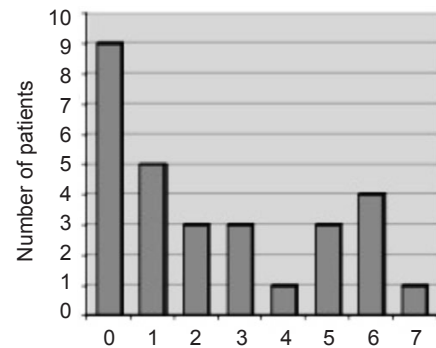


Figure 2. Number of plaques with some characteristic of vulnerability in each patient.

Table 1. Clinical characteristics and cardiovascular risk factors.

Total: n	2
Men: n (%)	21 (84)
Age (years)	62 \pm 8
Body mass index >25 kg/m ² : n (%)	20 (80)
Clinical presentation (n):	
Stable angina	14
Silent ischemia	4
Unstable angina (elevated troponin)	7 (4)
Smokers (yes/past/no): n	3/15/7
Hypertension: n (%)	17 (68)
Diabetes mellitus: n (%)	11 (44)
Hypercholesterolemia n (%)	6 (24)
(TC* >200 mg/dL):	
Hypertriglyceridemia n (%)	6 (24)
(>150 mg/dL):	
Elevated hs-CRP ** (>3 mg/L)	9 (36)
Creatinine >1 mg/dL: n (%)	1 (25)/4 (16)
women >1.1/men	

*TC, total cholesterol; ** hs-CRP: high sensitive C reactive protein.

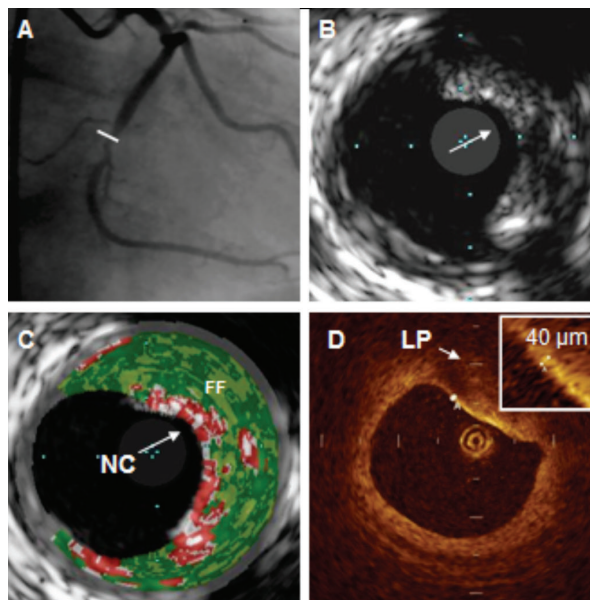


Figure 3. The same plaque is imaged with four different techniques. (A) Coronary angiography: significant lesion in the left circumflex artery. (B) IVUS: important plaque burden (arrow). (C) VH: predominant fibrofatty (FF) component and significant necrotic core (NC). (D) OCT: large lipid pool (LP) with a thin (<65 μ m) cap. Magnified view in the upper right corner.

(3 angiographically significant). A small thrombus was seen on 5 lesions (Figure 4D, E and F), all of them angiographically significant. Two fibrin rich thrombi were not attached to the intima. Two non-fibrin rich thrombi were attached to the intima (without plaque rupture) and were assumed to be secondary to erosion (Figure 4D and F).¹⁵ The remaining thrombus was not fibrin rich nor was attached to the intima.

A calcified nodule with a thin cap was found in 8 lesions (Figure 4C), 3 of them in the middle RC artery and 5 in different locations. Six had negative remodeling and 2 no remodeling. Three lesions with calcified nodule were significant. There were a total of 27 lesions with some OCT-derived possible characteristic of vulnerability.

Relationships between clinical data and possible features of vulnerability

Thirty-seven lesions (23 angiographically significant) were studied in 18 stable patients and 9 lesions (7 angiographically significant) in 7 unstable patients.

Fifteen patients, 4 of 7 (57%) unstable and 11 of 18 (61%) stable, had some possible vulnerable lesion. No significant difference in age (63 ± 15 vs. 60 ± 19) was found between patients with and without these lesions. No significant difference was to be seen in gender.

A significant necrotic core was found in 15 lesions. Twelve lesions were found in 8 of 18 stable patients (44%), and 3 lesions in 2 of 7 unstable patients (29%). OCT-derived TCFA was detected in 10 lesions. Four lesions were found in 4 of 18 (22%) stable patients and 3 lesions in 3 of 7 (43%) unstable patients. All the erosions and calcified nodules were found in stable patients. Four thrombi were found in 4 of 18 stable patients and one thrombus in one of 7 unstable patients (NS). The 3 women included in the study had intraluminal thrombi.

Patients with significant necrotic core had a higher body mass index (29.4 ± 6 vs. 26.1 ± 7) ($P=0.032$). No significant relationship was detected between other possible characteristics of vulnerability and body mass index. No significant relationship was found between vulnerability and diabetes, smoking or hypertension. The only individual lesion related with age was erosion: 71 ± 6 (with) vs. 62 ± 15 (without) ($P=0.038$).

Relationships between morphological and biochemical characteristics

No correlation was found between the presence of some characteristic of vulnerability in the plaques and troponin elevation prior to the procedure. Patients with angiographically significant lesions had higher levels of LDL (117 ± 24 vs. 103 ± 38) ($P=0.043$) and total cholesterol (191 ± 54 vs. 172 ± 24) ($P=0.001$) than those without. However, the percentage of cal-

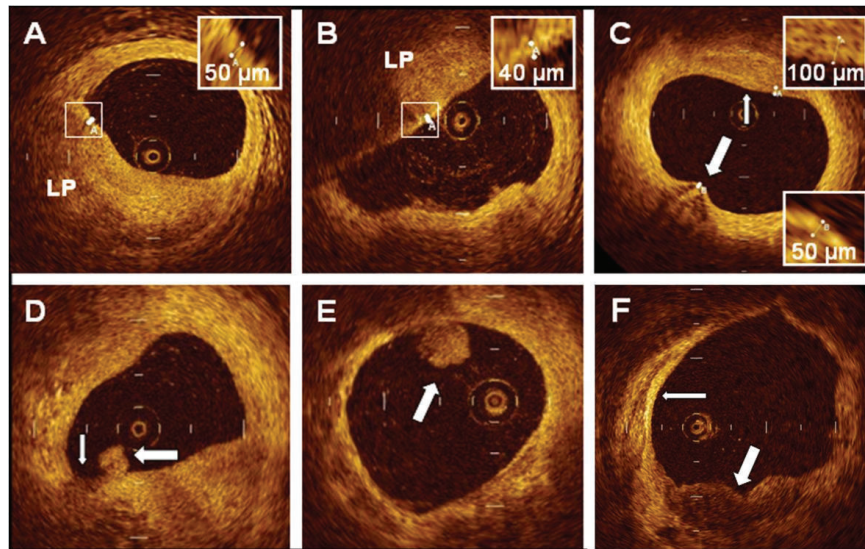


Figure 4. Different images with OCT. (A and B) The lipid pool (LP) with a thin ($<65 \mu\text{m}$) cap corresponds to a thin cap fibroatheroma (TCFA). (C) The thick arrow shows a calcified nodule protruding into the lumen with a thin cap, and the thin arrow a lipid pool with a cap $>65 \mu\text{m}$. (A, B and C) Measurements of the fibrous cap are amplified. (D) An erosion can be seen (thin arrow) as a dark image not covered by a fibrous cap. A displaced thrombus (thick arrow) is stuck on the right over a fibrous cap. (E) The arrow shows a thrombus not attached to the intima. (F) The thick arrow shows a mural thrombus in direct contact with the intima (compatible with erosion). The thin arrow shows a thick cap over a calcification.

cium in the atherosclerotic plaques was inversely related to the level of LDL-cholesterol. ($r=-0.57$, $P=0.022$)

Patients with significant necrotic core had higher levels of hs-CRP (0.466 ± 0.68 vs. 0.169 ± 0.22) ($P=0.019$) and triglycerides (134 ± 120 vs. 84 ± 100) ($P=0.040$). The higher the levels of hs-CRP, the larger the size of the necrotic core ($r=0.61$, $P=0.012$) and the smaller the amount of fibrosis ($r=-0.56$, $P=0.024$) in the plaque. Patients with calcified nodules had lower hs-CRP levels (0.19 ± 0.4 vs. 0.42 ± 0.06) ($P=0.040$). Patients with OCT-derived TCFA had lower levels of HDL (37 ± 15 vs. 52 ± 34) ($P=0.039$). When the entire group of patients with some characteristic of vulnerability was compared with the group of patients without any characteristic, no significant differences were found.

Complications of the procedure

No patient had serious complications or significant worsening of renal function after the entire procedure, including endovascular treatment in unstable patients. No patients had new troponin elevation after the procedure. Mean creatinine level changed from 0.98 ± 0.11 mg/dL before the procedure to 1.1 ± 0.13 mg/dL the following day. The mean time of radiation was 51 ± 38 minutes, and the amount of contrast used was 200 ± 35 mL. The mean time of the procedure was 62 ± 17 min. The radiation time was 9 min shorter in the last 8 patients and the duration of the proce-

cedure was 10 min shorter in the last 5 patients. These changes were due to a faster OCT pull-back, the non-occlusive technique and the learning curve.

Discussion

In this pilot study we have characterized *in vivo* the coronary plaques of a group of stable and unstable patients with different imaging modalities: IVUS-VH and OCT. We describe not only TCFA, but also other features that have been related to plaque vulnerability in previous necropsy studies:² significant necrotic core, erosions, thrombi and calcified nodules. Several groups have used OCT to study vulnerable plaques.^{10,11,22,23} The combination of IVUS plus OCT has already been used to detect definite TCFA,¹⁰ but other characteristics of vulnerable and complicated plaques have not been described. The combinations of imaging techniques make the *in vivo* identification of these characteristics possible. As the different features of vulnerability are detected with different techniques, the information obtained with each is complementary.

IVUS is a widely used technique that provides an accurate measurement of lesion remodeling.^{20,22} Although positive remodeling is not considered a characteristic of vulnerability, in general the most vulnerable lesions are large but not very occlusive,^{2,23} due to positive remodeling

index. Angiographic data from patients with ACS show that more than two-thirds of disrupted plaques are less than 50% occlusive to the coronary vascular lumen.²⁴ IVUS imaging studies have shown that culprit lesions are often associated with large plaque areas, even more so than stable lesions.²⁵ Because of positive remodeling, the plaque occupies less than 50% of the luminal area in 66% of cases.²⁶ In our study, the culprit lesion of unstable patients was not characterized because it was treated before starting the imaging study of the remaining arterial tree. Non-culprit lesions of unstable patients and lesions of stable patients had similar remodeling.

We only found 10 TCFA, mainly located in proximal and middle coronary artery segments and the majority associated with positive remodeling. HDL-cholesterol was lower in these patients. No other significant relationships were found, probably due to the small sample size. Significant necrotic core was related to high hs-CRP, that is a marker of instability, and the larger the size of the necrotic core, the higher the level of hs-CRP. However, the proportion of stable and unstable patients with necrotic core was not significantly different. Necrotic core was also related to body mass index and triglycerides. It is possible that hs-CRP and triglycerides were elevated in these patients due to high body mass index.²⁷ We found 8 calcified nodules with thin cap in stable patients with low hs-CRP level. Further studies are needed to verify whether it is a vulnerable or a benign lesion. In fact, post-mortem studies have found that rupture of calcified nodules is only responsible for a small percent of ischemic death.²

The significant correlation between each kind of lesion and clinical or biochemical variables has limited value due to the small number of cases analyzed. However, an interesting finding is that lesions with some characteristic of vulnerability were found in a big proportion (more than 50%) of both stable and unstable patients. This might indicate that not all of them are markers of instability, although follow-up studies are needed to investigate this.

Our study was carried out in a majority of stable patients. If follow-up studies demonstrate that some or all of these lesions are really precursors of ACS, we are still in time to start prophylactic treatment to avoid the acute event. This has a potential clinical impact, because stable angina is treated in a less aggressive way than unstable angina. Hence, if a patient in a stable clinical situation has vulnerable or complicated plaques, treatment should be more intensive (e.g. dual antiplatelet or new systemic or local therapy).

At present there are no clear data to predict which plaques are going to develop an ACS. However, the greater the number of studies, the higher the probability of clarifying this.

The ongoing PROSPECT study²⁸ is following-up patients studied with IVUS-VH plus palpography, not with OCT. Although OCT is probably the most helpful modality, the ideal study should be performed with both VH and OCT.

Limitations of the study

The first limitation is the small sample size. This prevents us from drawing definitive conclusions on the prevalence of vulnerable plaques and from establishing reliable correlations between clinical and biochemical variables.

Second, it is not possible to study all arteries in each patient and this provides only partial results. However, the invasive study of the coronary tree always has this limitation.

Conclusions

IVUS-VH and OCT detected coronary lesions with some characteristic of vulnerability (according to *post-mortem* studies) in 61% of stable and 57% of unstable patients. A significant necrotic core was mainly correlated with higher hs-CRP. Probably not all the described plaque characteristics are markers of instability. Follow-up studies are needed to investigate this.

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