EuroIntervention

Virtual histology and remodelling index allow *in vivo* identification of allegedly high-risk coronary plaques in patients with acute coronary syndromes: a three vessel intravascular ultrasound radiofrequency data analysis

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All authors have declared that there is no conflict of interest.

Abstract

Background: Virtual histology (VH) uses intravascular ultrasound (IVUS) radiofrequency spectral analysis to locally identify the morphology and composition of atherosclerotic plaques. We sought to explore *in vivo* the relation between IVUS-derived thin cap fibro-atheroma (IDTCFA) and remodelling index in patients with acute coronary syndromes using IVUS-VH.

Methods and results: Twenty-one patients (63 vessels) were enrolled. When compared to cross sectional areas (CSAs) without necrotic core in contact with the lumen (NCCL), CSAs with NCCL had a larger plaque burden 42.8±11.5% vs. 32.8±11.5%, p<0.001; higher overall necrotic core content [13.8±10.7% vs. 2.3±7.9% (p<0.001)] and calcified tissue [4.7±6.5 vs. 0.66±2.1% (p<0.001)]. On average there were 2 IVUS-derived thin cap fibro-atheroma (IDTCFA) per patient. Nearly half of the IDTCFAs had positive remodelling.

Conclusions: CSAs with NCCL had worse morphological profiles than those with no NCCL. The simultaneous and more detailed assessment of IDTCFA and remodelling index identifies a reduced number of allegedly high-risk plaques. The findings of this study may have important clinical implications, since they shed light into a possible method of identiying potentially high-risk plaques suitable for pharmacological and/or local treatment.

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Introduction

For the most part, acute coronary syndromes (ACS) are the consequence of the rupture of particular atherosclerotic plaques called thin-cap fibro-atheromas (TCFAs). These TCFAs have a thin fibrous cap, paucity of smooth muscle cells, heavy inflammatory infiltration of the cap, large necrotic core, positive remodelling and high strain[1-6]. Coronary plaque rupture is a frequent and unpredictable event that impacts the global burden of cardiovascular disease[7]. Indeed, coronary heart disease is expected to be the leading cause of disability-adjusted life-years in 2020[8]. Accordingly, many cutting-edge imaging techniques have recently been developed to help us better understand the atherosclerotic process. The first *in vivo* studies using such techniques were performed against the background of previous histopathological knowledge about morphological and compositional features related to plaques prone to rupture, so several studies have been published recently that mimic previous pathological findings[9-11]. Spectral analysis of the IVUS radiofrequency data (IVUS-VH) is emerging as a tool to assess plaque morphology and composition[12,13]. This combined assessment of remodelling and plaque characterisation might allow a more accurate and complete characterisation *in vivo* for allegedly high-risk plaques.

We thus sought to further explore *in vivo* the relation between compositional features of coronary atherosclerotic plaques, specifically IVUS-derived thin cap fibro-atheroma and remodelling index, in patients with acute coronary syndromes.

Methods

Patient selection

From January to May 2005, all patients with acute coronary syndromes admitted for coronary catheterisation and subsequent intervention were eligible if all three coronary vessels were suitable for IVUS interrogation (absence of extensive angiographic calcification and/or severe vessel tortuosity). Acute coronary syndrome encompasses unstable angina (UA) according to the Braunwald classification, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). The three-vessel IVUS-VH acquisition timing was as follows: in patients with UA/NSTEMI, acquisition was performed just after the interventional treatment; in patients suffering from STEMI it was done when the patient was symptom-free, without ECG changes and haemodynamically stable (defined as systolic blood pressure >90 mmHg without vasopressor or inotropic support, and with a heart rate of between 60 and 100 bpm). Informed written consent was obtained from all patients. Our local Ethics Committee approved the protocol.

IVUS-VH acquisition and analysis

Details regarding the validation of the technique on explanted human coronary segments and *in vivo* post-atherectomy have previously been reported[12,13]. Briefly, IVUS-VH uses spectral analysis of IVUS radiofrequency data to construct tissue maps that are correlated with a specific spectrum of the radiofrequency signal and assigned colour codes (fibrous [labelled green], fibro-lipidic [labelled greenish-yellow], necrotic core [labelled red] and calcium [labelled white])[12].

The IVUS-VH sampling rate during pull-back is gated to peak R-wave and is therefore dependent on heart rate. For instance, during constant heart rate of 60 bpm, then data will be collected every 0.5 mm. IVUS B-mode images were reconstructed from the RF data by customised software (IVUSLab Version 4.4, Volcano Therapeutics, Rancho Cordova, CA, USA). Semi-automated contour detection of both lumen and the media-adventitia interface was performed, and the RF data was normalised using a technique known as "Blind Deconvolution", an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus accounting for catheter-to-catheter variability[14,15]. Compositional data was obtained for every slice and expressed as mean percent for each component.

Quantification of the necrotic core in contact with the lumen (NCCL) and its angle was performed using MATLAB® (MathWorks, Natick, MA, USA).

Definitions used in this study

Necrotic core tissue in contact with the lumen, is defined as the presence of necrotic core tissue in direct contact with the luminal space and with no detectable overlying fibrous tissue; this is reported as (i) a continuous variable in mm^2, (ii) as a percent of the total plaque composition and (iii) as a percent out of the total necrotic core, (iv) as a binary variable considering the presence or absence of NCCL. In addition, the major confluent pool of NCCL was selectively quantified in terms of area in mm^2 and as a percentage of both the total plaque composition and the total necrotic core. The angle (measured from the gravity centre of the lumen) occupied by the entire NCCL was measured as well as the specific angle occupied by the major confluent NCCL. (Figure 1)

Plaque burden (PB), is defined as $EEM_{area}-Lumen_{area}/EEM_{area} \times 100$, where EEM refers to external elastic membrane.
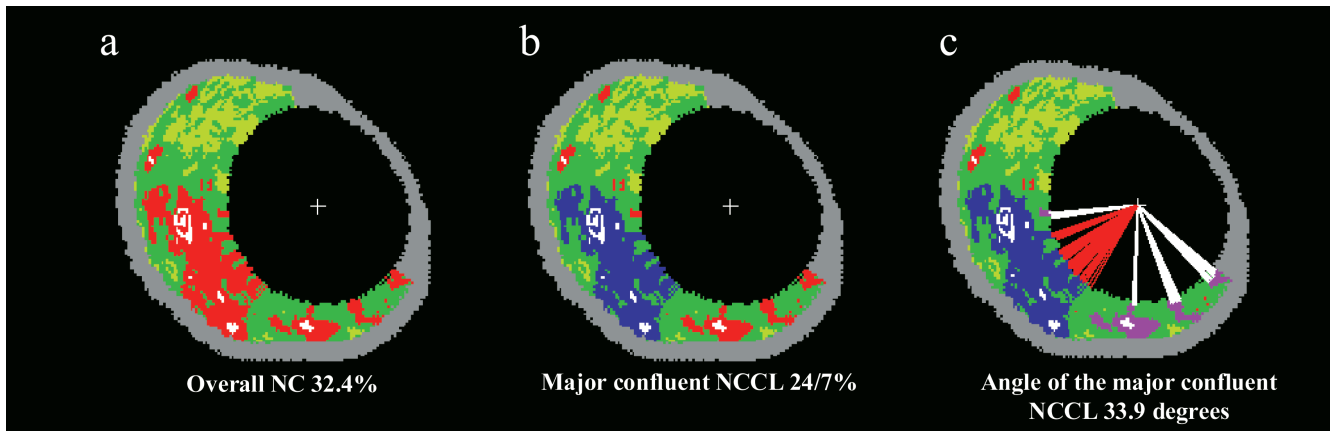
Figure 1. An example of selective quantification of the necrotic core in contact with the lumen. (a) The original IVUS-VH cross-sectional area; (b) Modification using the VH tool to selectively quantify the major confluent necrotic core that is in direct contact with the lumen. (c) Measurement of the angle occupied by the entire necrotic core in contact with the lumen (white and red lines) and specifically the angle occupied by the major confluent necrotic core in contact with the lumen (red lines).

Remodelling was assessed by means of the remodelling index (RI), expressed as the EEM CSA at the site of minimum luminal area divided by the reference EEM CSA as previously described[11,16,17].

The reference site was ≤10 mm proximal to the selected lesion[18]. There were no major side branches between the MLA and reference sites. We defined positive remodelling as RI ≥ 1.05 and negative remodelling as

RI ≤ 0.95. Values in between were considered neutral (no remodelling). IVUS-derived TCFA (IDTCFA)[9], is defined as a lesion fulfilling the following criteria in at least 3 consecutive CSAs: 1) plaque burden ≥ 40%; 2) confluent necrotic core ≥ 10%[19] in direct contact with the lumen in the investigated CSA (Figure 2). All consecutive CSAs having the same morphologic characteristics were considered as part of the same IDTCFA lesion.
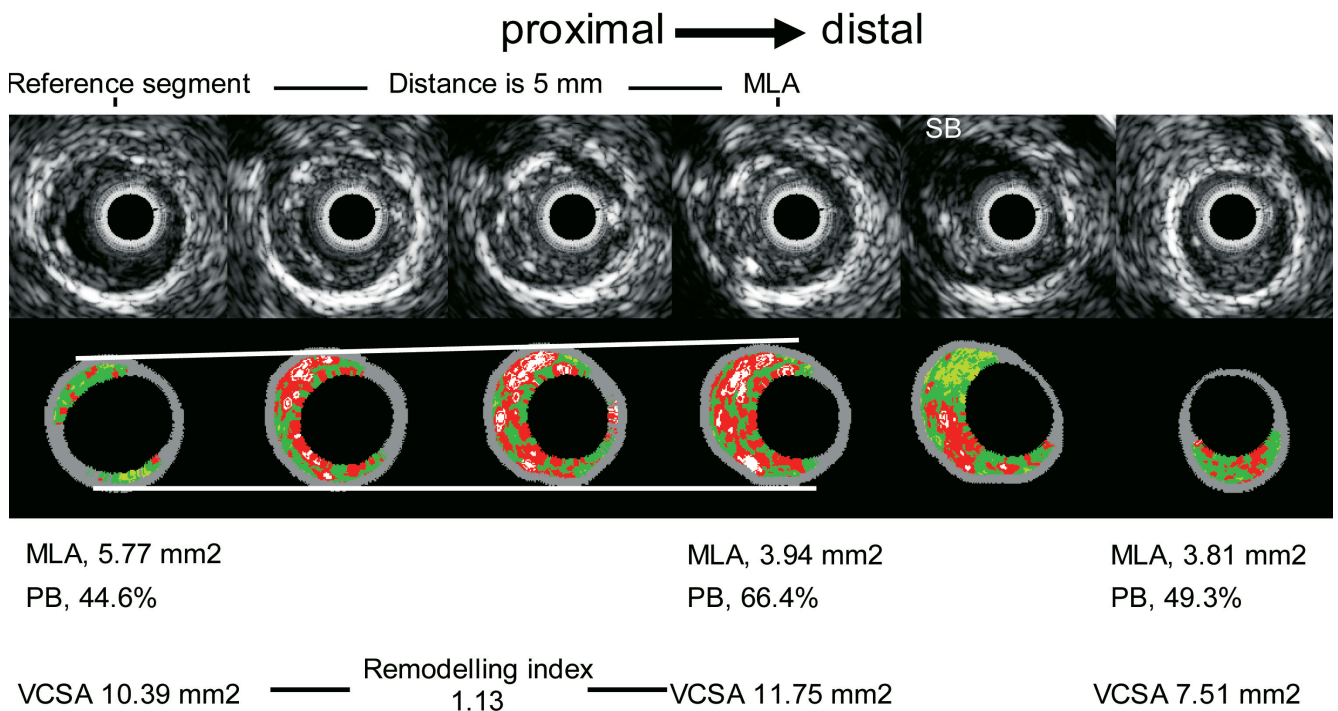

Figure 2. The figure shows the IVUS grey scale and the corresponding IVUS-VH frames of an IVUS derived thin cap fibro-atheroma (four central frames) and the proximal and distal reference segment in which the remodelling index was calculated. MLA, minimum luminal area; PB, plaque burden; VCSA, vessel cross sectional area.

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as means ±SD. A two-sided p value of less than 0.05 indicated statistical significance. Assumptions for normality were checked after transformation based on a p-value >0.20 at Kolmogorov-Smirnov test and by visual assessment of Q-Q plots of residuals. Accordingly, log transformation was performed on the variables with skewed distribution.

To compare CSAs with and without NCCL, in a General Estimating Equations model, with binomial distribution and a logit link function, cases were regarded as a random factor (as we had multiple observations for each patient); we also allowed for an autoregressive correlation structure and the vessel was a fixed factor in the model. Statistical analyses were performed with use of SPSS software version 11.5.

Results

Twenty-one (63 vessels) consecutive patients were included in this study. The baseline characteristics of the patient population are depicted in Table 1. The mean age was 52.9±7.8 years, most being male patients (71.4%). Sixty-six percent of the patients presented with acute myocardial infarction. The culprit vessel was the left anterior descending (LAD) in 47.6%, the left circumflex (LCX) in 23.8% and the right coronary artery (RCA) in 28.6% of the patients. The mean length of the IVUS pull-back was 45.7±22.9 mm.

IVUS-VH findings

A total of 6,351 CSAs were analysed with IVUS-VH. Necrotic core in contact with the lumen was found in 71.7% (4556/6351) of CSAs. These CSAs had a mean area of necrotic core in contact with the lumen of 0.59±0.72 mm^2 which corresponds to 13.8±10.7% of

Table 1. Baseline characteristics, n=21

Age, yrs (mean±SD)	52.9±7.8
Male %	71.4
Body mass index, kg/m^2 (mean±SD)	27.3±4.2
Diabetes mellitus %	33.3
Hypertension %	33.3
Family history of CHD %	42.9
Current smoking %	71.4
Hypercholesterolaemia %	33.3
Previous ACS %	14.3
Previous PCI %	28.6
Clinical presentation %	
Unstable angina/Non-ST-segment elevation MI	33.3
ST-elevation MI	66.7
Culprit vessel %, n=21	
Left anterior descending	47.6
Left circumflex	23.8
Right coronary artery	28.6

SD, standard deviation; CHD, cardiovascular heart disease; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; MI, myocardial infarction.

the total plaque area; on average 53.8±35.2% of the total amount of necrotic core present in a CSA was in contact with the lumen and the angle occupied by the necrotic core in the luminal circumference was 30.3±34.8°. Nearly all the geometrical and compositional parameters of the CSA with NCCL were significantly different compared with CSAs without necrotic core in contact with the lumen (Table 2). Specifically, CSAs with NCCL had a higher plaque burden compared to CSAs without NCCL, 42.8±11.5% vs. 32.8±11.5%, p<0.001 and more necrotic core and calcified tissue compared to the ones without NC in contact with the lumen, 13.8±10.7% vs. 2.3±7.9% (p<0.001) and 4.6±6.4 vs. 0.59±2.1% (p<0.001) respectively.

Table 2. Compositional and geometrical analysis of CSAs with necrotic core in contact with the lumen.

	NC No contact (1795 CSAs)		NC Contact (4556 CSAs)		
	Mean	SD	Mean	SD	p value
Calcified mm^2	0.02	0.06	0.21	0.38	0.03
Calcified %	0.59	2.1	4.6	6.4	<0.001
Fibrous mm^2	1.5	1.7	2.6	1.8	0.01
Fibrous %	66.3	17.4	62.7	12.0	0.03
Fibrolipid mm^2	0.68	0.85	0.84	0.86	0.86
Fibrolipid %	30.7	18.0	18.9	11.6	0.60
Necrotic core mm^2	0.04	0.12	0.59	0.72	0.005
Necrotic core %	2.27	7.9	13.8	10.7	<0.001
Vessel CSA mm^2	16.7	5.6	18.0	6.6	0.24
Lumen CSA mm^2	11.2	4.2	10.3	4.6	0.29
Plaque CSA mm^2	5.5	2.9	7.6	3.4	0.006
Plaque eccentricity	0.11	0.12	0.18	0.16	0.65
Plaque burden %	32.5	11.2	42.8	11.5	<0.001

NC, necrotic core; CSA, cross sectional area.

Overall, there were 805 (12.7%) CSAs with confluent NCCL >10%; among these only 430 CSAs had a PB >40% (Table 3).

Table 3. Number of CSAs according to the amount of confluent necrotic core in contact with the lumen and plaque burden >40%.

	Overall, n=6351	CSAs with PB >40%, n=2886
Confluent NCCL >10%	805(12.7%)	430(14.9%)
Confluent NCCL >15%	385(6.1%)	198(6.9%)
Confluent NCCL >20%	218(3.4%)	105(3.6%)
Confluent NCCL >25%	125(2%)	44(1.5%)
Confluent NCCL >30%	73(1.1%)	23(0.8%)

NCCL, necrotic core in contact with the lumen; CSA, cross-sectional area; PB, plaque burden

IVUS-derived thin cap fibro-atheroma

A total of 42 IDTCFAs were detected in the 21 patients. However, 13 patients had at least one IDTCFA in their coronary tree (38.1% of the population did not have any IDTCFA). Thus, on average there were 2 IDTCFAs per patient. Seventeen IDTCFAs were found in the LAD, 12 in the LCX and 13 in the RCA. In 7 patients at least one

other IDTCFA was found in a different vessel and in 13 vessels more than one IDTCFA was found in the same vessel (Table 4).

Table 4. Description of the multifocal aspect of IDTCFA.

	IDTCFA n=42
No. patients with:	
One	13
Two	9
Three	8
Four or more	5
No. of vessels with:	
One	23
Two	13
Three	6
Four or more	1
No. of patients with one IDTCFA in at least one other vessel	7

CSA, cross-sectional area; IDTCFA, IVUS-derived thin cap fibro-atheroma

The mean IDTCFA lesion length was 4.8±2.8 mm (Range: 0.95-13.5 mm) and the remodelling index was 1.09±0.21. In three IDTCFAs it was not possible to measure the remodelling index due to lack of reference segment; two of them were located in the proximal LAD, so the only segment without disease proximal to the lesion was the left main artery. Five (11.9%) IDTCFAs had negative remodelling, 14 (33.3%) no remodelling and 20 (47.6%) had positive remodelling. The IDTCFAs were divided into three different categories according to the largest confluent necrotic core in contact with the lumen, largest confluent NCCL < 20%, NCCL between 20-30% and NCCL >30%. Subsequently, the remodelling index was plotted against these three categories (Figure 3). The overall mean necrotic core was 26.5±9.7%, and the major area of confluent NC that was in contact with the lumen was 12.2±8.0% which repre-
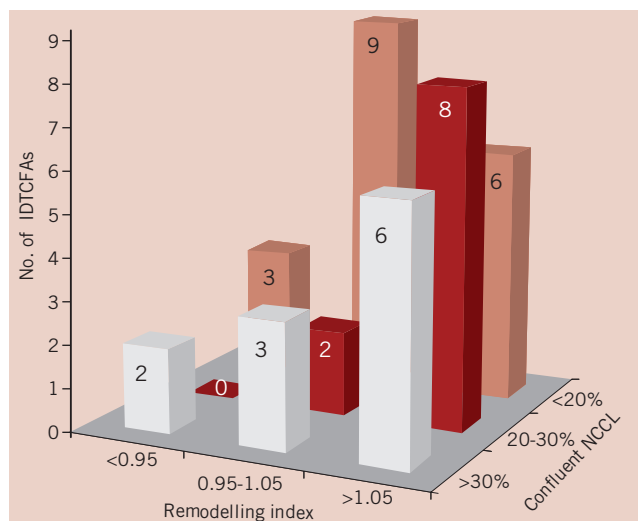

Figure 3. Bar graph shows the number of IVUS-derived thin cap fibro-atheroma according to the largest confluent necrotic core in contact with the lumen (NCCL) and the remodelling index. It seems that among the IDTCFAs there are different degrees of disease, possibly with different likelihoods of rupture.

sented 44.9±21.2% of the total amount of NC present in the CSA. The circumference occupied by the confluent NCCL was 27.6±17.5°. The mean plaque burden was 50.3±8.5, whilst the vessel CSA and lumen CSA were15.4±6.2 mm2 and 7.6±3.3 mm^2 respectively (Table 5).

Table 5. Characteristics of IVUS-derived thin cap fibro-atheroma.

	IDTCFA, n=42	
	Mean	**SD**
Calcified mm^2	0.35	0.38
Calcified %	7.6	7.0
Fibrous mm^2	2.5	1.7
Fibrous %	54.4	10.6
Fibrolipid mm^2	0.56	0.65
Fibrolipid %	11.5	8.5
Necrotic core mm^2	1.2	0.81
Necrotic core %	26.5	9.7
Major confluent NC in contact with the lumen		
– Area mm^2	0.68	0.58
– % out of the total NC	45.0	21.2
– % out of the total PCSA	12.2	8.0
– Angle of the NC (degrees)	27.6	17.5
Vessel CSA mm^2	15.4	6.2
Lumen CSA mm^2	7.6	3.3
Plaque CSA mm^2	7.8	3.4
Plaque eccentricity	0.21	0.16
Plaque burden %	50.3	8.5
Length (mm)	4.8	2.8
Remodelling index	1.1	0.21

NC, necrotic core; CSA, cross sectional area; PCSA, plaque CSA; SD, standard deviation.

Discussion

The main findings of this study that included 21 patients (63 vessels) with acute coronary syndrome are: 1) on average there were 2 IDTCFAs per patient; 2) after treatment of the culprit lesion, 38.1% of the population did not have any IDTCFA; 3) CSAs with NC in contact with the lumen were more obstructive and with larger vessel CSA than their counterparts without NC in contact with the lumen; 4) CSAs with NC in contact with the lumen had also larger necrotic core and calcified tissue compared to the ones without NC in contact with the lumen; 5) Nearly half of the IDTCFAs had positive remodelling.

To date, there is no single isolated marker of vulnerability that can accurately and precisely identify atherosclerotic plaques at risk of rupture. On the contrary, it seems that the *in vivo* simultaneous assessment of acknowledged high-risk atherosclerotic plaque characteristics may improve the accuracy to reliably identify vulnerable plaques. For the first time IDTCFA and remodelling index are assessed in an *in vivo* three vessel IVUS-VH based study in patients with acute coronary syndrome.

Trying to understand the atherosclerosis process has continued for more than a century, and while many paradigms have lost importance, others still remain. Specifically, although vast information with respect to the pathophysiology of acute coronary syndromes has been published, only a few concepts are today generally accepted. First, the former belief that acute coronary syndromes originate exclusively from flow-limiting stenoses has shifted to well-defined histological plaque phenotypes. These plaques have particular characteristics, such as large necrotic core, thin fibrous cap, inflammation within the cap and positive remodelling[4,12,20-22]. Nevertheless, to date, the natural history of lesions with these characteristics remains unknown and the limited knowledge about their eventual prognosis is provided by retrospective histopathological studies[7,23]. Second, inflammation plays an important part in the development and growth of such plaques, and most importantly in triggering unpredictable rupturing events[24]. Third, the multifocal distribution of vulnerable plaques has been proven by means of pathology[1], angiography[25], angioscopy[20], IVUS[26], palpography[27] and lately IVUS-VH[9]. This latter concept is once again demonstrated in this study, where in 33.3% (7/21) of the patients IDTCFAs were present in at least two vessels. Moreover, in 31.7% of the vessels, two or more IDTCFAs were detected.

Spectral analysis of IVUS radiofrequency data has been used as a tool to assess plaque composition and remodelling[11,12], since they are acquired in one single pull-back, simultaneous and complementary information can be retrieved. The previous manuscript from our group reporting the incidence of IDTCFA is essentially similar from the methodological point of view, but dramatically different from the quantitative point of view. So in the first report by Rodriguez-Granillo et al[9], one of the criteria was the presence of NC>10% in a CSA with some NC in contact with the lumen, without considering its distribution along the luminal circumference (spotty or confluent). Thus, the main difference with the approach used in this report is the fact that the CSAs were included only if the necrotic core was confluent and this pool of NC represented more than 10% of the tissue present in the CSA and was in direct contact with the lumen. This different methodology may impact on the reported incidence of vulnerable plaque, but it offers a definition which is closer to the pathological one. Nevertheless, the inability to precisely measure the thickness of the fibrous cap makes our observations a surrogate of the pathological TCFA.

Positive remodelling has been associated with an unstable clinical presentation[17,28] and with characteristic pathological[6] and IVUS-VH[11] lesion types. In line with these previous reports, the remodelling index found in this study shows the outward growth of these types of plaques. Some lipid lowering trials using conventional IVUS have suggested that there is a change in "composition" after a period of treatment[29], whilst another with a similar design reported a change in the remodelling index[18]. IVUS-VH offers the opportunity to follow-up these lesions and to correlate longitudinally and simultaneously the composition and the change in the remodelling index. It seems that among IDTCFAs there is different degree of disease. Not all of them have positive remodelling. The only opportunity to know if there is a different degree of risk among the same type of lesion is to look back into the pathological studies to learn which

TCFAs have been undergone rupture. It is clear that ruptured plaque have more necrotic core, macrophage infiltration, calcification, less smooth muscles cells and more positive remodelling than TCFAs[30]. We can then conclude that those IDTCFAs having abundant necrotic core with positive remodelling have a higher risk, and it turns out that in this study these are few in number.

The clinical implications of these findings are manifold. First, the capability of simultaneously assessing more than one of the different acknowledged features of "high-risk" plaques could potentially enhance the prognostic value of the invasive detection of vulnerable plaque. Second, this combined assessment can potentially identify very high-risk plaques, thereby lowering the number of vulnerable plaques that deserve to be followed and ultimately treated.

Limitations

Although we have included all consecutive patients with three vessel IVUS assessment in a defined period of time, the sample size is small. In general, the more severely diseased part of the vessel was stented before IVUS acquisition eliminating the analysis of potentially the most pathological region of interest.

The inferior axial resolution of IVUS-VH in comparison to histology remains a major handicap, but is partially compensated by the higher sampling rate of the ultrasonic approach when compared to the pathologic.

Conclusions

Cross sectional areas with necrotic core in contact with the lumen had a worse morphological profile than the ones without NC in contact with the lumen. The simultaneous assessment of IDTCFA and remodelling index identifies a reduced number of high-risk plaques. The findings of this study have potentially important clinical implications, since for the first time it sheds light into the possibility to follow these plaques after pharmacological treatment and/or to treat them locally.

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