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Morphology of coronary artery lesions assessed by virtual histology intravascular ultrasound tissue characterization and fractional flow reserve

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Abstract Fractional flow reserve (FFR) is an index of the physiological significance of a coronary stenosis. Patients who have lesions with a FFR of >0.80, even optimally treated with medication, have however a MACE rate ranging from 8 to 21%. Coronary plaques at high risk of rupture and clinical events can be also identified by virtual histology intravascular ultrasound (IVUS-VH) as plaques with high amount of necrotic core (NC) abutting the lumen. Aim of this exploratory study was to investigate whether the geometry and composition of lesions with FFR $\leq$ 0.80 were different from their counterparts. Fifty-five consecutive patients in whom FFR was clinically indicated on a moderate angiographic lesion, received also an imaging investigation on the same lesion with IVUS-VH. Data on plaque geometry and composition was analyzed. Patients were subdivided in two groups according to the value of FFR (> or $\leq$0.80). Lesions with a FFR $\leq$ 0.80 ($n = 17$) showed a slightly larger plaque burden than those with FFR > 0.80 ($n = 38$) (54.6 $\pm$ 0.7% vs. 51.7 $\pm$ 0.7% $P = 0.1$). In addition, they tend to have less content of necrotic core than their counterparts (14.2 $\pm$ 8% vs. 19.2 $\pm$ 10.2%, $P = 0.08$). No difference was found in the distribution of NC-rich plaques (fibroatheroma and thin-capped fibroatheroma) between groups (82% in FFR $\leq$ 0.80 vs. 79% in FFR > 0.80, $P = 0.5$). Although FFR $\leq$ 0.80 lesions have larger plaque size, they do not differ in composition from the ones with FFR > 0.80. Further exploration in a large prospective study is needed to study whether the lesions with FFR > 0.80 that are NC rich are the ones associated with the presence of clinical events at follow-up.

Keywords Intravascular ultrasound virtual histology · Fractional flow reserve

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Introduction

The presence of myocardial ischemia is an important risk factor for an adverse clinical outcome [1]. Revascularization of stenotic coronary lesions that induce ischemia can improve patient's functional

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status and outcome [1, 2]. For stenotic lesions that do not induce ischemia, however, the benefit of revascularization is less clear, and medical therapy alone is likely to be equally effective [3, 4].

Fractional flow reserve (FFR) is an index of the physiological significance of a coronary stenosis and is defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow [5]. A FFR value of 0.80 or less identifies ischemia-causing coronary stenoses with accuracy of more than 90% [5, 6]. Plaques at high risk of rupture and provoking coronary events appear to have high amount of necrotic core [7–10] and this feature can be readily identified by virtual histology intravascular ultrasound (IVUS-VH) [11].

Aim of our study was to explore whether the geometry and composition of lesions with FFR $\leq$ 0.80 were different from their counterparts.

Methods

In this exploratory study, all consecutive patients, exhibiting an angiographically moderate lesion on one coronary vessel, admitted from January 2009 to January 2010 in whom FFR was clinically indicated [12, 13], underwent on the same lesion an IVUS-VH analysis to investigate the relationship between functional and morphological/compositional lesion characteristics.

Quantitative coronary angiography analysis

Quantitative coronary angiography (QCA) analyses were performed by one experienced independent observer, blinded to FFR, IVUS-VH and clinical data, using the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). The following QCA parameters were computed: computer-defined minimum lumen diameter (MLD), reference vessel diameter (RVD) obtained by the interpolate method, and percentage diameter stenosis [14].

IVUS-VH acquisition and plaque-type classification

The IVUS was performed using the Eagle Eye 20 MHz catheter (Volcano Corp., Rancho Cordova, California) with an automatic continuous pullback at a rate of 0.5 mm/s (30 frames/sec) at level of the lesion evaluated by FFR. Grayscale images and radiofrequency data required for VH analysis were acquired during the same pullback and raw radiofrequency data capture gated to the R wave (In-Vision Gold, Volcano). The VH processing was performed offline with pcVH 2.1 software (Volcano Corp., Rancho Cordova, California) that permits semi-automated contours detection and provides the compositional structure of the vessel. Quantitative IVUS measurements included vessel area, lumen area, plaque area (vessel area minus lumen area) and plaque burden ([plaque area/vessel area] $\times$ 100). For the radiofrequency-IVUS analyses, four tissue components (necrotic core—red; dense calcium—white; fibrous—dark green; and fibrofatty—light green) were identified with autoregressive classification systems. Each individual tissue component was quantified and color-coded in IVUS cross sections, as previously described [7, 15].

Lesions were classified by 2 experienced and independent observers, blinded to FFR data, based on plaque composition in 3 consecutive frames within the lesion, as previously described [16]: pathological intimal thickening (PIT), thin-cap fibroatheroma (TCFA), calcified fibroatheroma (CAFA), thick-capped fibroatheroma (ThFA), calcified thick-cap fibroatheroma (CATHFA), fibrotic plaque and fibrocalcific plaque [17, 18]. In case of disagreement, a consensus was reached between the two observers. PIT consisted of mainly a mixture of fibrous and fibrofatty tissue plaque with <10% confluent necrotic core and <10% confluent dense calcium. TCFA was a fibroatheroma without evidence of a fibrous cap: >10% confluent necrotic core with >30° necrotic core in contact with the lumen. Calcified fibroatheroma was a fibroatheroma with >10% confluent dense calcium. ThFA was a fibroatheroma (>10% of confluent necrotic core) with a definable fibrous cap. CATHFA was a ThFA with >10% confluent dense calcium. Fibrotic plaque (FT) consisted of mainly fibrous tissue with <10% confluent necrotic core, <15% fibrofatty tissue and <10% confluent dense calcium. Fibrocalcific plaque (FC) was composed of nearly all fibrous tissue and dense calcium with <10% confluent necrotic core. All the plaques with >10% of necrotic core were also classified as NC-rich plaques.

FFR evaluation

The FFR evaluation was done according to the current guidelines [12, 13]. The FFR was measured with a coronary pressure guidewire (Radi, St.Jude Medical, Uppsala, Sweden) at maximal hyperemia induced by intravenous adenosine, administered at 140 μg/kg/min through a periferical vein. FFR is calculated as the mean distal coronary pressure (measured with the pressure wire) divided by the mean aortic pressure (measured simultaneously with the guiding catheter) during maximal hyperemia [19]. In the case of diffuse atherosclerosis punctuated by focal areas of more severe stenosis, or in the case of more than one stenosis within the same artery, pressure pullback recordings during hyperemia were performed as described previously [13, 20]. In addition, whenever another significant lesion was detected within the same vessel it was recommended by protocol that the FFR measurements should be performed after this lesion had been treated.

Statistical analysis

Categorical variables were expressed as counts and percentage. Group differences of categorical variables were compared using chi-square or fisher-exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation (SD). The normal distribution of the variables was explored by Kolgomorov-Smirnov test. As the variables were not normally distributed, comparison between groups was done by non parametric tests. A P value of <0.05 was considered significant, and all tests were two-tailed. Data were analyzed with SPSS version 16.0 software (SPSS Inc., Chicago, IL).

Results

Baseline clinical and angiographic characteristics

Fifty-five consecutive patients were enrolled in the study. Table 1 shows their clinical and angiographic characteristics. All the patients included had only one-vessel disease, that was investigated by FFR and IVUS-VH analyses. In particular 17 out of these patients (31%) showed a FFR ≤ 0.80 and 13 patients (23%) received stent implantation on the lesion evaluated by FFR. The remaining 4 patients did not receive any treatment for the following reasons: the minimum lumen area by IVUS was >4 mm^2 in 3 patients and the FFR was 0.79 in 1 patient. The 38 patients with a FFR ≥ 0.80 did not receive any revascularization treatment and were treated by medical therapy.

QCA analysis confirmed that all the lesions included in the analysis were angiographically moderate lesions (46% mean stenosis), for which the FFR evaluation is indicated according to guidelines. Patients with a FFR ≥ 0.80 exhibited higher RVD and MLD than those patients with a FFR ≤ 0.80 (Table 1).

IVUS geometrical analysis (Table 2)

Plaque burden was slightly larger for those lesions with a FFR ≤ 0.80 (54.6 ± 0.7% vs. 51.7 ± 0.7% $P = 0.1$) accompanied with a reduction in lumen area (7.1 ± 1.8 mm^2 vs. 7.9 ± 2.4 mm^2, $P = 0.1$) and without expansion of the vessel area as compared to their counterparts (16.0 ± 5.0 mm^2 vs. 16.5 ± 4.4 mm^2, $P = 0.4$). Minimum lumen area was lower for those lesions with a FFR ≤ 0.80 than those with a FFR > 0.80 ($P = 0.07$).

IVUS-VH analysis

Table 2 shows the compositional IVUS-VH data. Plaques with FFR ≤ 0.80 showed higher relative content of fibrofatty tissue ($P = 0.02$) and a trend towards a lower relative content of necrotic core ($P = 0.08$) compared to plaques with FFR > 0.80.

Plaque classification yielded good concordance between the two observers ($\kappa = 0.85$). Overall, we found 9 PIT, 2 FC, 7 FA, 6 CaFA, 9 TCFA and 22 CaTCFA (Fig. 1). No difference was found in the distribution of VH-plaque type between the two groups (Fig. 2). NC-rich plaque distribution was also not different between groups (82% in FFR ≤ 0.80 vs. 79% in FFR > 0.80, $P = 0.5$).

Discussion

The major finding of this analysis is that, although larger plaques are associated with FFR ≤ 0.80, VH-plaque composition and VH-plaque type are not

Table 1 Clinical and angiographic characteristics

	Patients ($n = 55$) Lesions ($n = 55$)	FFR > 0.80 (38 patients)	FFR ≤ 0.80 (17 patients)	P value
Age (years)	61 ± 10	61 ± 9	60 ± 12	0.24
Mean ± SD (n)				
Men (%)	83	81	88	0.70
Smokers (%)	56	55	58	1.00
Diabetes (%)	12	15	5	0.41
Hypertension requiring medication (%)	63	65	58	0.76
Hyperlipidaemia requiring medication (%)	69	68	70	1.00
Stable angina (%)	69	71	65	0.75
Unstable angina (%)	30	29	35	0.63
Target vessel (%)				0.98
Left anterior descending	65	65	64	
Left circumflex	16	15	18	
Right coronary artery	18	20	18	
QCA analysis				
MLD (mm)	1.66 ± 0.37	1.76 ± 0.34	1.43 ± 0.34	0.03
RVD (mm)	3.14 ± 0.52	3.25 ± 0.54	2.90 ± 0.39	0.03
% stenosis	46.1 ± 0.9	45.2 ± 0.8	49.0 ± 0.1	0.16
FFR	0.84 ± 0.08	NA	NA	NA

SD standard deviation, *QCA* quantitative coronary angiography, *MLD* minimum lumen diameter, *RVD* reference vessel diameter, *FFR* fractional flow reserve

different between lesions with FFR more or equal/less than 0.80.

From previous studies it is known that patients, who have lesions with a FFR > 0.80, if optimally treated with medication, have a good prognosis up to 5-years [4]. However, the MACE rate of these patients may range from 8 to 21% [21–25]. We set out this exploratory study to investigate whether plaque composition could be one of the reasons to explain this occurrence of events if these lesions are left untreated, based on FFR findings. Interestingly, QCA already discriminates in our analysis the lesions with a FFR ≤ 0.80 which have smaller MLD and RVD compared with lesions with a FFR ≥ 0.80. However, it appears that although FFR ≤ 0.80 lesions are more stenotic and have larger size, they do not differ in composition from the ones with FFR > 0.80 and left untreated. Rogers et al. [26] demonstrated a heterogeneous VH-plaque type morphology with prevalence of TCFA in FFR-negative lesions. In our study, comparing FFR negative and positive lesions, we found that the relative content of NC seems to be higher in lesions with a FFR > 0.80 ($P = 0.08$). This could be a possible explanation of MACE for those patients with angiographically intermediate lesions, left untreated as no functionally significant by FFR (>0.80) [21]. In addition, lesions with FFR ≤ 0.80 exhibited higher fibrofatty tissue content than those lesions with FFR ≥ 0.80 ($P = 0.02$). This tissue, corresponding to lipids without necrosis, is namely present in PIT, that have been shown able to evolve in VH-fibroatheroma [27].

From pathological studies it is known that specific coronary plaques characteristics, such thin fibrous cap, paucity of smooth muscle cells, heavy inflammatory infiltration of the cap and large necrotic cores correlate with fatal ischemic events [28]. The recent PROSPECT trial has also shown that thin-capped fibroatheroma, identified by IVUS-VH, is a strong independent predictor of events at 3-year follow-up [11]. Angiographic studies before and after myocardial infarction showed that pre-existing lesions at the sites of myocardial infarction are not usually accompanied by hemodinamically significant stenosis [29]. In sudden coronary death, at least 50% of the thrombosis occurred at lesion sites with ≤50%

Table 2 IVUS-VH data

	FFR > 0.80 (n = 38 lesions)	FFR ≤ 0.80 (n = 17 lesions)	P value
IVUS-VH data			
Mean plaque area (mm^2)	8.6 ± 2.6	8.9 ± 3.5	0.8
Plaque burden (%)	51.7 ± 0.7	54.6 ± 0.7	0.1
Mean lumen area (mm^2)	7.9 ± 2.4	7.1 ± 1.8	0.1
Minimum lumen area (mm^2)	5.6 ± 2.3	4.6 ± 1.2	0.07
Mean vessel area (mm^2)	16.5 ± 4.4	16.0 ± 5.0	0.4
Fibrous tissue (mm^2)	2.7 ± 1.4	3.0 ± 1.8	0.6
Fibrous tissue (%)	54.5 ± 10.7	57.3 ± 6.7	0.2
Fibrofatty tissue (mm^2)	0.8 ± 0.8	1.2 ± 1.1	0.07
Fibrofatty tissue (%)	15.1 ± 11.1	21.5 ± 10.8	0.02
Necrotic core tissue (mm^2)	0.9 ± 0.5	0.7 ± 0.4	0.2
Necrotic core tissue (%)	19.2 ± 10.2	14.2 ± 8.0	0.08
Dense calcium (mm^2)	0.5 ± 0.4	0.3 ± 0.3	0.1
Dense calcium (%)	11.0 ± 8.3	6.8 ± 4.8	0.1
VH plaque distribution			0.7
PIT, n (%)	6 (15)	3 (17)	
FC, n (%)	2 (8)	0 (0)	
FA, n (%)	4 (10)	3 (17)	
CaFA, n (%)	5 (13)	1 (8)	
TCFA, n (%)	6 (15)	3 (17)	
CaTCFA, n (%)	15 (39)	7 (41)	

Data are expressed as mean ± standard deviation. *FFR* fractional flow reserve, *PIT* pathological intimal thickening, *FC* fibrocalcific plaque, *FA* fibroatheroma, *CaFA* calcified fibroatheroma, *TCFA* thin-cap fibroatheroma, *CaTCFA* calcified thin-cap fibroatheroma

angiographic diameter reduction [30]. However, we cannot elucidate from our study whether the lesions with FFR > 0.80 that are NC rich (77% of them) are the ones associated with the presence of clinical events at follow-up. This hypothesis needs further exploration in a larger prospective study.

On the other side, Kubo et al. [27] showed recently that there are various possible pathways in the evolution and stabilization of NC-rich plaques. At 12-month follow-up they found that most of the NC-rich plaques healed or stabilized. The mechanism of healing is not well established. The transformation of hematoma and/or thrombus into fibrous muscular tissue and the formation or increase in thickness of the fibrous cap could lead to plaque stabilization [31]. Some studies have proposed that a silent rupture or a plaque rupture proximal to a lesion might lead to mural thrombus and subsequent formation of a fibrotic cap over the TCFA [32, 33]. This could be the natural evolution of the NC-rich plaques for lesions with a FFR more than 0.80, as the good prognosis of these patients. In addition, it is noteworthy to consider that a large minimum lumen area could also favor a silent NC-rich plaque rupture, allowing a coronary flow sufficient to avoid a clinical event. In our study, we found, indeed, a lower minimal lumen area in FFR ≤ 0.80 lesions as compared to FFR > 0.80 lesions. This hypothesis also would need further exploration in a larger prospective study.

Finally, it is important to highlight that IVUS-VH and FFR are two different ways to evaluate the significance of a coronary plaque. While FFR is a standardized method evaluating the functional significance of an intermediate coronary stenosis, IVUS-VH analysis provides information on the plaque size and on its tissue characterization through its back-scattering signal. As virtual histology is a sound-based imaging modality using the radiofrequency data to compute 4 different tissue types, it suffers from all limitations as any other ultrasound-derived techniques. While the use of FFR to decide the percutaneous treatment of a coronary lesion has been widely described and correlated with long-term prognosis [13, 34], the use of VH to decide a percutaneous treatment of a coronary plaque is not

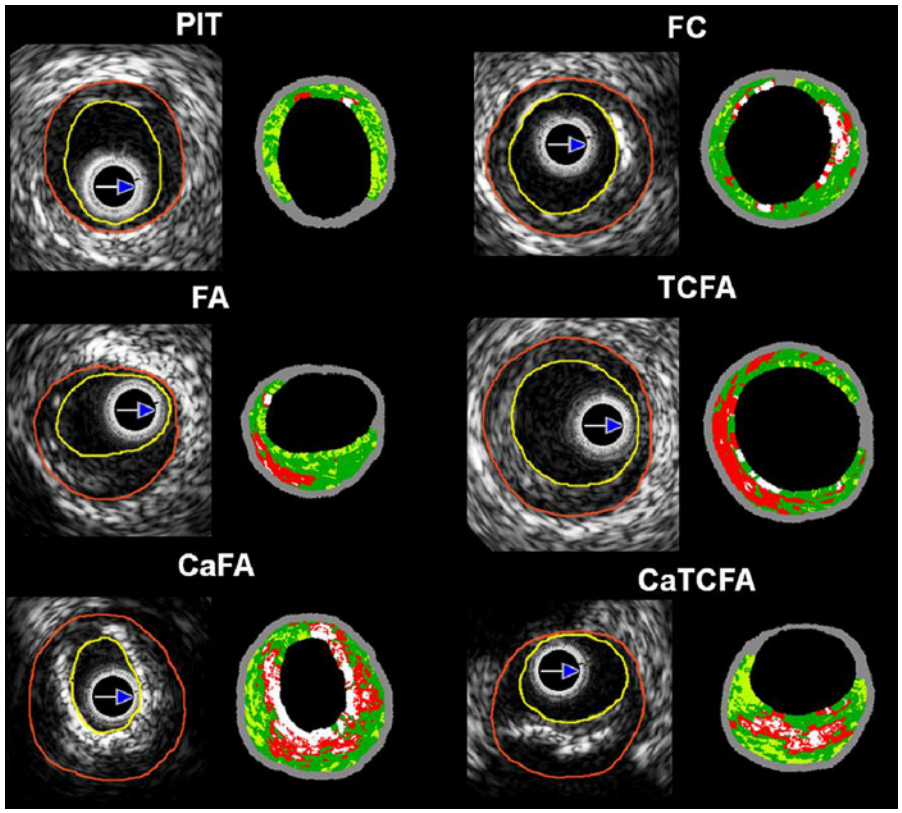

Fig. 1 Examples of various type of VH-plaque found in the analysis with the corresponding IVUS appearance. Lumen contour (*yellow line*) and vessel contour (*red line*) are shown. In the VH images, necrotic core is coded as *red*, dense calcium as *white*, fibrous tissue as *dark green* and fibrofatty tissue as *light green*. *PIT* pathological intimal thickening, *FC* fibrocalcific plaque, *FA* fibroatheroma, *TCFA* thin-cap fibroatheroma, *CaFA* calcified fibroatheroma, *CaTCFA* calcified thin-cap fibroatheroma

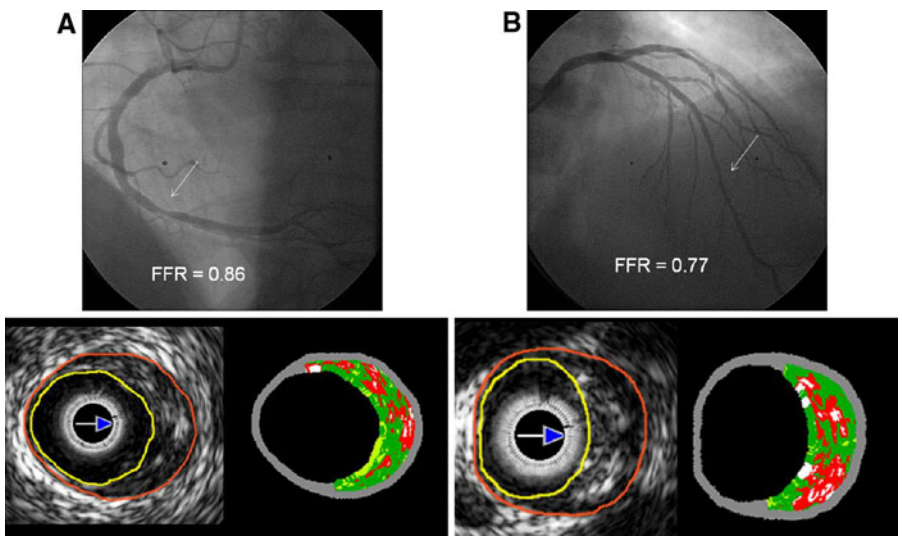

Fig. 2 Examples of two different lesions (white arrows) with a FFR > 0.80 (*panel A*) and ≤ 0.80 (*panel B*), both showing a FA VH-plaque type. In the IVUS images *red* and *yellow* contours indicate vessel and lumen contours, respectively

well investigated yet. The SECRITT-I trial is ongoing to test the efficacy of preventive treatment of a NC-rich plaque with a self-expanding stent, that allows the formation of a fibrous cap [35].

Limitations

This is a registry study and included a small number of patients. No clinical or angiographic follow-up are available. Our findings only focused on ambiguous/equivocal lesions were the use of FFR was considered of value in the clinical decision process. Whether other lesions causing less significant stenosis have different composition as compared with hemodinamically significant lesions will require additional studies.

Conclusions

Coronary lesions with FFR more or less than 0.80 are not different in terms of plaque composition and virtual histology plaque types from their counterparts. The hypothesis of whether a preventive treatment might be required for those patients who have a NC-rich plaque with FFR > 0.80 needs to be further explored.

Conflict of interest None of the authors have any conflict of interest to declare.

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