Int J Clin Exp Med 2016;9(12):23375-23385
www.ijcem.com /ISSN:1940-5901/IJCEM0026703

Original Article

Virtual histology intravascular ultrasound in assessment of intermediate coronary lesions for guidance of interventional therapy

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Received February 26, 2016; Accepted June 4, 2016; Epub December 15, 2016; Published December 30, 2016

Abstract: To assess role of virtual histology intravascular ultrasound (VH-IVUS) in characterizing plaque composition and guiding interventional therapy for patients with intermediate coronary lesions (ICL). Enrolled patients (n = 86) with quantitative coronary angiography (QCA) confirmed ICL were classified into acute coronary syndrome (ACS) group and stable angina (SA) group. Coronary lesions were subjected to IVUS and VH-IVUS to identify patients for interventional therapy. Incidence of major adverse cardiovascular events (MACE) was analyzed with 6 month follow-up. Main plaque compositions of ACS group were necrotic core (NC) and fibro-fatty tissue (FF), and SA group were dense calcium (DC) and fibrotic (FI) on VH-IVUS (all $P < 0.01$). LDL levels were positively correlated with FF area ($P = 0.028$); HDL level was negatively correlated with FF area and NC area ($P = 0.040$ and $P = 0.020$, respectively). At the minimum lumen area (MLA), gray-scale IVUS showed higher performance in diagnosing lesions with DSR of 60%-70% and > 70% than QCA (both $P < 0.05$). Significant differences were found in the PA, PB, VAD, LAD, DSR, EI and RI (all $P < 0.05$), while no significant difference in occurrence of total MACEs were found between intervention group and non-intervention group ($P > 0.05$). Gray-scale IVUS is useful to define ICL extent and nature for interventional therapy guidance; IVUS-VH showed improved diagnosis of vulnerable plaque, and particularly in characterizing plaque necrosis for interventional therapy guidance for patients with significantly increased necrotic component by combining with clinical lipid levels.

Keywords: Quantitative coronary angiography, intravascular ultrasound, virtual histology intravascular ultrasound, intermediate coronary lesions, interventional therapy, diameter stenosis rate, plaque composition, major adverse cardiovascular events

Introduction

Intermediate coronary stenosis rrefers to coronary lesions of intermediate stenosis severity visually estimated on coronary angiography (CAG) with diameter stenosis (DS) of 40%-70% [1]. Previous evidence showed that 6% of the intermediate coronary lesions (ICL) develop into acute coronary events requiring interventional therapy within 1 year, and 87% of culprit plaques are previously confirmed as ICL [2]. In addition, a prospect study suggested that 11.6% of major adverse cardiovascular events (MACE) are mostly resulted from nonculprit lesions at sites of angiographically mild coronary-artery stenosis [3]. The CAG is previously considered as gold standard for diagnosis and treatment of coronary heart disease (CHD), but is restricted due to 2-dimensional representation with overestimated lumen area and underestimated lesion extent and DS, especially in distinguishing ICL [4, 5]. Study conducted by Latacz *et al.* revealed that symptomatic ICL patients underwent interventional therapy simply according to the angiographic findings showed higher incidence in stent restenosis and more frequent recurrent angina compared with pharmacological treatment [6]. Therefore, we need to further screen patients with ICL who are at increased risk of future coronary events for appropriate medical therapy.

Intravascular ultrasound (IVUS) can display real-time cross-sectional images of coronary artery, and is widely used for evaluating lesion severity, optimizing stent implantation and sub-

Table 1. Subject clinical baseline data (n (%), ± s)

Clinical data	
Age	59.4 ± 12.2
Male	65 (73)
Smoking history	28 (60.2)
Hypertension	47 (54.6)
Family history of coronary heart disease	6 (7.0)
Diabetes	13 (28.2)
Total cholesterol (mmol/L)	4.12 ± 0.68
Triglyceride (mmol/L)	1.85 ± 0.48
LDL (mmol/L)	3.01 ± 0.72
HDL (mmol/L)	1.24 ± 0.14
hs-CRP (mg/L)	4.24 ± 1.23
Glycosylated hemoglobin (%)	6.45 ± 0.14
Serum creatinine (umol/L)	74.45 ± 16.89
Uric acid (umol/L)	365.7 ± 95.2
Medicine usage	
Statins	41 (89.1)
ACEI/ARB	27 (58.7)
β-blockers	37 (80.4)
Vascular lesion part	158
Left main coronary artery	10 (6.3)
Rami anterior descendens	65 (41.1)
Circumflex artery	50 (31.7)
Right coronary artery	33 (20.9)

Note: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; LDL, low density lipoprotein; HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

sequently reducing adverse cardiovascular events [7, 8]. IVUS guided percutaneous coronary intervention (PCI) shows improved clinical outcomes, which is especially found in patients with complex lesions admitted with acute coronary syndromes (ACS) [9]. ICL on IVUS show a moderate correlation to fractional flow reserve (FFR) values useful for guiding revascularisation in ICL, and IVUS minimum lumen area (MLA) may be used as an alternative to FFR when assessing the need for intervention in ICL [10]. However, QCA-, CTA-, and IVUS-derived quantitative anatomic measurements correlated with FFR in intermediate-to-severe lesions and CTA-derived cut-points were similar to respective measurements on QCA and IVUS and had similar or better diagnostic performance compared with IVUS [11]. A recent large observational study reported that IVUS-guided PCI was not associated with improved long-term survival compared with standard angiography-guided PCI [12]. Grey-scale IVUS is useful for assessing coronary artery morphometry and quantifying the atheroma, but with significant limitations in assessing plaque composition [13]; while quantitative information provided by virtual histology (VH)-IVUS can differentiated plaque composition into atherosclerotic plaque as fibrotic (FT), fibro-fatty (FF), dense calcium (DC), and necrotic core (NC) [14]. VH-IVUS, reported by a previous study, is considered as reference standard in ICL by prospective validation [15]. The VH-IVUS volumetric assessment may provide better relationship between plaque morphology and the FFR values relative to gray-scale IVUS 2-dimensional analysis for coronary intermediate to obstructive stenosis lesions [16]. VH-IVUS has been used to investigate effect of lipid-lowering therapy on coronary atherosclerotic plaques and to study the dynamic natural history of coronary artery lesion morphology [14, 17, 18]. Therefore, the present study aims to assess the value of VH-IVUS in making clinical decisions about interventional therapy of in patients with ICL.

Materials and methods

Study subjects

Between July 2011 and May 2015, 86 patients with QCA confirmed ICL (QCA diameter stenosis, 40%-70%) were enrolled from cardiac catheter laboratory in the Department of Cardiology of the First Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, China. Inclusion criteria: (1) age ranging from 18- to 80-years old; (2) clinically suspected or confirmed coronary heart disease (CHD); (3) electrocardiogram (ECG) indicated myocardial ischemia or cardiac color Doppler ultrasound indicated ventricular segmental wall motion abnormalities. Exclusion criteria: valvular heart disease, congenital heart disease, myocardiosis, coronary bypass surgery, cardiac function IV, coronary artery diameter ≤ 2 mm, aspirin and clopidogrel intolerance, heparin and contrast agent allergy, coagulation disorders or expected survival time < 1 years. Intraoperative exclusion criteria: triple vessel disease, left main coronary artery or chronic total occlusion. The enrolled patients were divided into acute coronary syndrome (ACS) group and stable angina (SA) group according to clinical manifestations and electrocardiogram (ECG) changes.

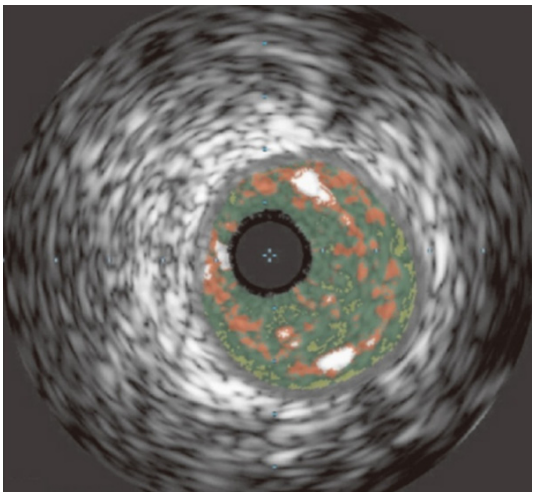

Figure 1. Virtual histology intravascular ultrasound (VH-IVUS) ultrasonographic: deep green (fibrous tissue, FT); light green (fibro-fatty, FF); white (dense calcium, DC); and red (necrotic core, NC).

The clinical baseline data were collected, including sex, age, smoking, diabetes, of hypertension history, family history, etc. (**Table 1**). Accessory examination: routine blood test, liver and kidney function, blood lipids, glycosylated hemoglobin, serum creatinine, uric acid, hs-CRP, medicine usage, etc. After admission, patients were treated with aspirin 100 mg and clopidogrel 75 mg once a day, followed by preoperative one-time aspirin 200 mg + clopidogrel 225 mg treatment, while giving statins, ACEI/ARB, beta blockers and other treatment. After approved by the Ethics Committee of the First Affiliated Hospital of Wannan Medical College, and written informed consents were obtained from the study subjects.

QCA examination

QCA was performed with an angiography machine (Siemens, Erlangen, Germany) via the radial artery or femoral artery approach using the Judkins technique. The extent of coronary stenosis was analyzed by taking more than 2 vertical positions. The most severe lumen stenosis was selected, and the reference vessel diameter (RVD) is about 5 mm far from the near-end and far-end of the lesion. Minimal lumen diameter (MLD) and the diameters of the near-end and far-end of the lesion were measured. Diameter stenosis (DS) rate = (RVD-MLD)/RVD ×100%. The QCA results were analyzed by 2 experienced doctors in the Department of Cardiology, and QCA diameter stenosis of 40%-70% was considered as ICL. Interventional therapy was taken into considerations in coronary lesions with stenosis degree ≥ 70% combined with clinical indicators, and selective interventional therapy was conducted in coronary lesions with stenosis degree in the range of 40%-70% combined with other objective indicators [19].

IVUS examination

QCA confirmed ICLs were further examined by IVUS (Volcano Therapeutics, USA). Heparin (100 U/kg) was injected through an arterial sheath surrounding the catheter before image acquisition, conventional injection of nitroglycerin (100~200 ug) in the coronary artery was conducted for the prevention of vascular spasm. The IVUS catheter was then delivered to the far-end of the lesion, and slowly retraced (0.5 mm/s), and images were real-time recorded for image analysis.

Gray scale-IVUS quantitative analysis

Minimum lumen Cross-section area (MLA) (lumen-intima junction) and external elastic membrane area (EEMA) were selected for measurement, the reference vessel segments were selected as the segments within 10 mm distal and proximal to the lesion site of the same blood vessel, but before any large side branch. Plaque area (PA) = EEMA-MLA. Plaque burn (PB) = (PA/EEMA) ×100%. Vessel average diameter (VAD) = (maximum diameter + minimum diameter of total cross-section)/2. Lumen average diameter (LAD) = (lumen maximum diameter + lumen minimum diameter. Diameter stenosis rate (DSR) = [(VAD-LAD)/VAD] ×100%. Eccentricity index (EI) = (maximum plaque thickness-minimum plaque thickness)/maximum plaque thickness. EI < 0.5 indicates concentric plaques, while EI > 0.5 indicates eccentric plaques. Plaque remodeling index (RI) = lesion EEMA/mean EEMA of proximal and distal references. RI = 0.95~1.05 indicates remodeling, RI > 1.05 as positive remodeling, and RI < 0.95 as negative remodeling. Delayed intervention treatment were suggested for patients with minimum lumen area ≥ 4.0 mm^2 and DSR < 70%. Positive interventional therapy was given to patients with minimum lumen area < 4.0 mm^2 and DSR ≥ 70%.

Table 2. Patient baseline data in the SA group and the ACS group

	SA group (n = 38)	ACS group (n = 48)	P
Male	28 (73.7)	37 (77.1)	0.462
Age	62.1 ± 9.8	63.4 ± 10.2	0.830
Hypertension history	20 (52.6)	27 (52.3)	0.098
Smoking history	9 (23.7)	14 (29.1)	0.212
Family history of coronary heart disease	2 (5.3)	4 (8.3)	0.579
Diabetes history	7 (14.6)	6 (15.8)	0.447
Total cholesterol (mmol/L)	4.10 ± 0.64	4.13 ± 0.72	0.841
Triglyceride (mmol/L)	1.83 ± 0.45	1.86 ± 0.50	0.760
LDL (mmol/L)	2.77 ± 0.70	3.19 ± 0.68	0.007
HDL (mmol/L)	1.27 ± 0.12	1.20 ± 0.14	0.018
hs-CRP (mg/L)	4.24 ± 1.13	4.23 ± 1.32	0.341
Glycosylated hemoglobin (%)	6.44 ± 0.13	6.45 ± 0.15	0.746
Serum creatinine (umol/L)	72.20 ± 16.0	76.23 ± 17.52	0.274
Uric acid (umol/L)	351.91 ± 98.24	376.61 ± 92.29	0.234

Note: ACS, acute coronary syndrome; SA, stable angina; LDL, low density lipoprotein; HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

Table 3. Gray-scale intravascular ultrasound (IVUS) examination results in the SA group and the ACS group

	SA group (n = 38)	ACS group (n = 48)	P
PA (mm^2)	7.54 ± 2.20	8.07 ± 2.33	0.282
PB (%)	68.88 ± 9.86	71.02 ± 10.91	0.349
VAD (mm)	4.02 ± 0.58	4.09 ± 0.65	0.657
LAD (mm)	1.62 ± 0.42	1.55 ± 0.41	0.439
DSR (%)	59.70 ± 8.80	62.29 ± 6.80	0.127
EI	1.14 ± 0.34	1.42 ± 0.45	0.002
RI	1.07 ± 0.31	1.33 ± 0.37	< 0.001
Plaque ruptures (n)	3 (5.3)	6 (12.5)	0.488

Note: ACS, acute coronary syndrome; SA, stable angina; PA, plaque area; PB, plaque burn; VAD, vessel average diameter; LAD, lumen average diameter; DSR, diameter stenosis rate; EI, eccentricity index; RI, remodeling index.

VH-IVUS qualitative index

The components of the plaque tissues were determined according to the echo characteristics of ultrasonic: deep green (fibrous tissue, FT); light green (fibro-fatty, FF); white (dense calcium, DC); and red (necrotic core, NC). Mixed plaques were identified as plaques with the echo characteristics of the above-mentioned plaques (**Figure 1**). The echo of main components of plaques less than vascular adventitia echo are regarded as soft plaques. Fibrous plaques, mixed plaques and calcified plaques are collectively referred as hard plaques [20]. Plaque rupture: the integrity intima destruction, lacuna of the plaques is connected with lumen, and plaques show echo characteristics of blood flow. NC ≥ 20% indicates interventional therapy.

PCI interventional therapy

The ACS group and the SA group were divided into intervention group and non-intervention group. Percutaneous coronary intervention (PCI) was carried out for coronary lesions with diameter stenosis ≥ 70% (n = 15) on IVUS, and coronary lesions with diameter stenosis < 70% but plaque necrosis area ≥ 20% (n = 2, ACS). Success criteria for PCI: coronary artery residual stenosis < 20% on IVUS. The aspirin (100 mg/d) was administered for patients without PCI for a long time. After PCI, patients were treated with aspirin (100 mg/d) for a long time and clopidogrel (75 mg/d) for at least one year. According to the secondary prevention guidelines for CHD, patients were treated with β-blockers, nitrates, angiotensin-converting enzyme inhibitors and statins.

Follow-up

Patients were followed up for 6 months after surgery by outpatient or telephone for prognosis, and the major cardiovascular events (recur-

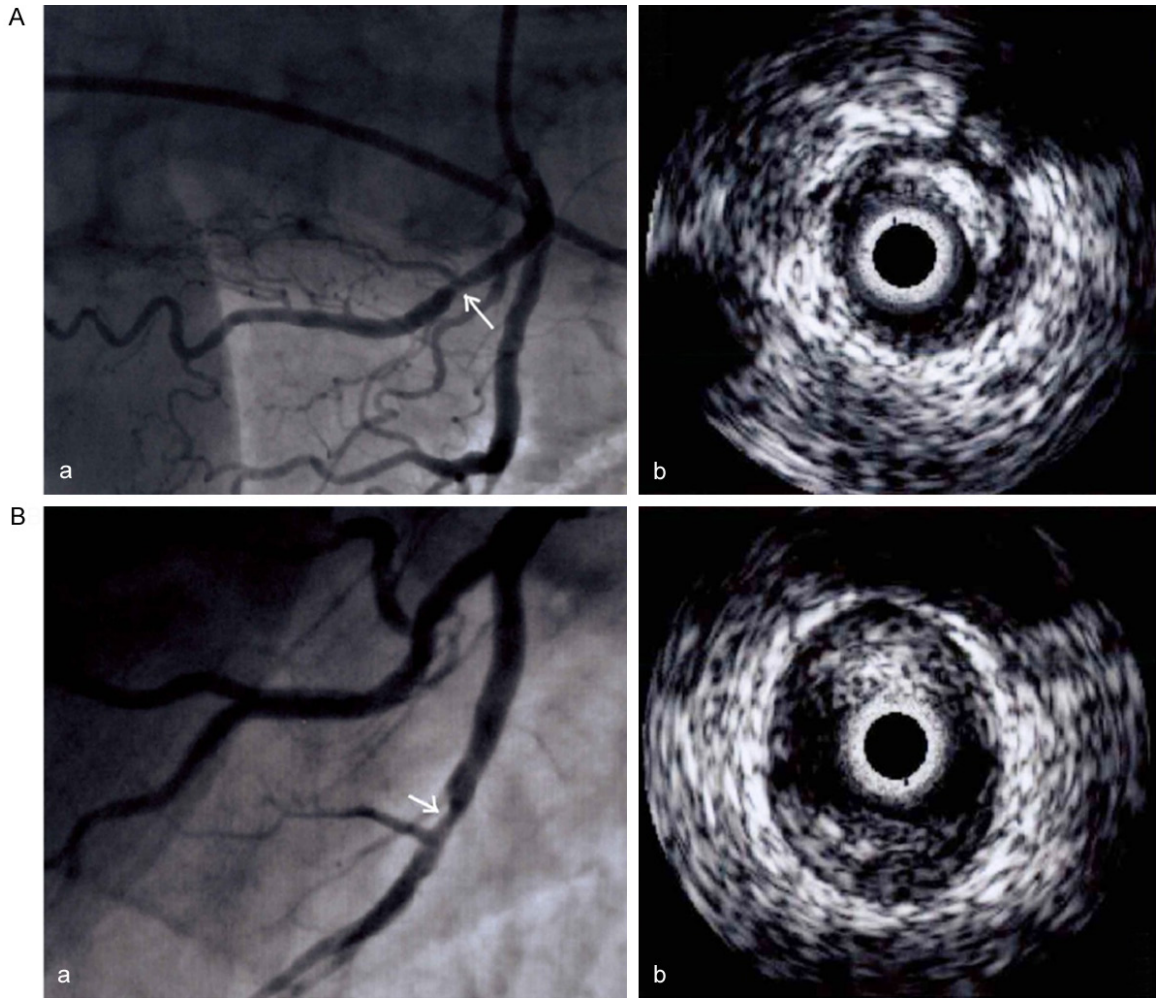

Figure 2. The intermediate coronary lesions examined by gray-scale intravascular ultrasound (IVUS): (A-a), the proximal segment of the anterior descending branch (arrowhead) showed a diameter stenosis of about 60% on quantitative coronary angiography (QCA) in a patient with stable angina; (A-b), minimal lumen area MLA position of the patient with stable angina on gray-scale IVUS, external elastic membrane area (EEMA) = 10.28 mm^2, plaque area (PA) = 6.38 mm^2, plaque burn (PB) = 62%, vessel average diameter (VAD) = 4.09 mm, and lumen average diameter (LAD) = 2.14 mm; (B-a), the proximal segment of the anterior descending branch (arrowhead) showed a diameter stenosis of about 60% on QCA in a patient with acute coronary syndrome; (B-b), MLA position of the patient with acute coronary syndrome on gray-scale IVUS, EEMA = 11.13 mm^2, PA = 7.73 mm^2, PB = 69%, VAD = 3.78 mm, and LAD = 2.20 mm.

rent angina, myocardial infarction, sudden cardiac death, and revascularization), time of onset, therapeutic measures, medicine usage and risk factor control were recorded.

Statistical analyses

Categorical variables were expressed as frequencies/percentages, and compared with chi-square test. Continuous variables were expressed as $\bar{X} \pm s$, and compared with *t*-test. Correlation analysis was performed with Pearson test. SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was applied to statistical analysis. A *P* value of 0.05 indicated statistically significant.

Results

Baseline data

In the SA group (n = 38), 24 cases were male (63.2%), the mean age was 62.1 ± 9.8 years; In the ACS group (n = 48), 41 cases were male (63.2%), the mean age was 63.4 ± 10.2 years. There were no obvious differences in gender, age, hypertension history, smoking history, diabetes history, total cholesterol, high sensitive C

Table 4. Virtual histology intravascular ultrasound (VH-IVUS) examination results in the SA group and the ACS group

	SA group (n = 38)	ACS group (n = 48)	P
FT area	29.06 ± 9.27	22.26 ± 6.94	< 0.001
FF area	25.60 ± 7.56	39.30 ± 7.85	0.030
DC area	27.17 ± 8.94	21.84 ± 6.64	0.002
NC area	18.17 ± 4.65	26.59 ± 7.45	< 0.0001
TCFA (%)	7 (18.4)	20 (41.7)	0.021

Note: ACS, acute coronary syndrome; SA, stable angina; FT, fibrous tissue; FF, fibro-fatty; DC, dense calcium; NC, necrotic core; TCFA, thin cap fibroatheroma.

reactive protein, glycosylated hemoglobin, serum creatinine and uric acid between the SA group and ACS group (all $P > 0.05$). Higher LDL level and lower HDL were observed in the ACS group than those in the SA group (all $P < 0.05$) (**Table 2**).

Gray-scale IVUS examination results

The gray-scale IVUS examination showed that the EI and RI of culprit plaques in the ACS group were greater than those in the SA group (all $P < 0.01$). The plaque ruptures were detected in 9 cases (SA = 3; ACS = 6), but without marked difference between the ACS and SA groups. No distinctive differences in PA, DSR, VAD, LAD, DS (%), or PB were found between the ACS group and the SA group (all $P > 0.05$) (**Table 3**; **Figure 2**).

VH-IVUS examination results

IVUS-VH examination showed that stenosis lesions were mainly differentiated in FT and DC in the SA group ($P < 0.01$), and presented with thicker plaque fibrous cap (FC); and stenosis lesions were mainly differentiated in FF and NC in the ACS group ($P < 0.05$), and presented with vulnerable plaque feature, namely, thin cap fibroatheroma (TCFA) (**Table 4**; **Figure 3**).

Correlation analysis of LDL and HDL with plaque composition

LDL levels were positively correlated with FF area ($r = 0.237$, $P = 0.028$), presented with non-significant negative correlation with DC and FT area, and presented with non-significant positive correlation with NC. HDL levels were negatively correlated with the FF and NC area ($r = -0.223$, $P = 0.040$; $r = -0.251$, $P = 0.020$), and presented with non-significant positive correlation with DC and FT area (**Table 5**).

Gray-scale IVUS guided interventional therapy

QCA results and IVUS results on lumen DSR at the narrowest segment were analyzed, the minimal luminal area site with DSR < 50% was diagnosed in 1 site with on IVUS, which was significantly lower than that of QCA (n = 16) ($P < 0.05$); DSR of 50%-60% in 40 sites on IVUS, which was also significantly lower than that of QCA (n = 54), but without significant difference; and DSR of 60%-70%/ > 70% in 30/15 sites on IVUS, which was also significantly higher than those of QCA (n = 15/0) (both $P < 0.05$) (**Table 6**).

PCI was carried out for coronary lesions with DSR ≥ 70% (n = 15) on IVUS, and coronary lesions with DSR < 70% but plaque necrosis area ≥ 20% (n = 2). In the intervention group, the RI and EI in the ACS group were higher than that in the SA group (both $P < 0.05$), which showed that the majority of the ACS group was eccentric plaques (**Table 7**).

Follow up analysis

In the SA group, 2 cases were lost to follow-up (94.7%), 6 cases received stent implantation, 4 cases suffered from recurrent angina, there was no sudden cardiac death or revascularization events, and 4 cases had adverse cardiovascular events. In the ACS group, 2 cases were lost to follow-up (95.8%), 11 cases received stent implantation, 5 cases suffered from recurrent angina, there was no sudden cardiac death or revascularization events, and 8 cases had adverse cardiovascular events. No significant difference in the occurrence of total MACEs between the e ACS group and the SA group (8/46 vs. 4/36, $P = 0.489$).

Compared to the non-intervention group, no visibly difference in total MACEs was found in the intervention group (4/17 *vs.* 8/65, $P = 0.328$). There were no differences in the total adverse cardiovascular events in the ACS and SA sub-groups in the intervention group (1/6 *vs.* 3/11, $P = 0.622$), similar association was found in the non-intervention group (3/30 *vs.* 5/35, $P = 0.853$). IVUS can guide the interventional therapy of ICLs (**Table 8**).

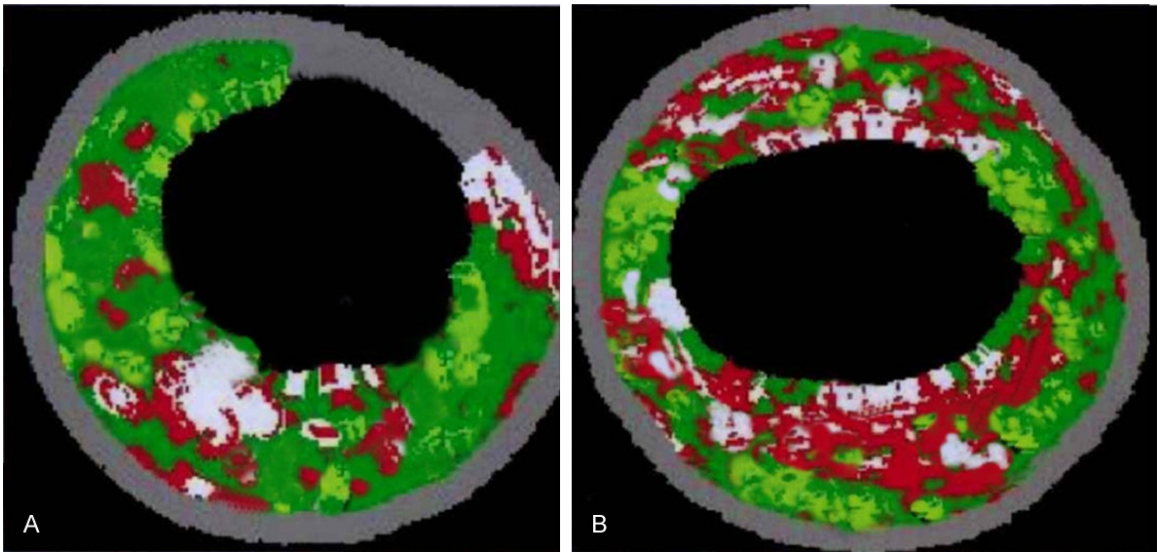

Figure 3. The intermediate coronary lesions examined by virtual histology intravascular ultrasound (VH-IVUS): A. VH-IVUS image in a patient with stable angina, fibrous tissue (FT) cross-section area (CSA)% = 52.24%, dense calcium (DC) CSA% = 11.09%, fibro-fatty (FF) CSA% = 15.22% and necrotic core (NC) CSA% = 21.15%; B. VH-IVUS image in a patient with acute coronary syndrome, FT CSA% = 14.79%, DC CSA% = 11.71%, FF CSA% = 29.45% and NC CSA% = 44.05%.

Table 5. Correlation analysis of LDL and HDL with plaque composition

	FT area		FF area		DC area		NC area	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
LDL	-0.151	0.165	0.237	0.028	-0.137	0.208	0.074	0.496
HDL	0.041	0.710	-0.223	0.040	0.026	0.810	-0.251	0.020

Note: LDL, low density lipoprotein; HDL, high density lipoprotein; FT, fibrous tissue; FF, fibro-fatty; DC, dense calcium; NC, necrotic core.

Table 6. The comparison of QCA and IVUS in the diagnosis of different DSR of the same lesion

Group	< 50%	50%-60%	60%-70%	> 70%
QCA	16 (18.60)	55 (63.95)	15 (17.44)	0 (0.00)
IVUS	1 (1.16)*	40 (46.51)	30 (34.88)*	15 (17.44)*

Note: DSR, diameter stenosis rate; QCA, quantitative coronary angiography; IVUS, intravascular ultrasound; *compared with QCA group, $P < 0.05$.

Discussion

Lesions with positive remodeling on CTA are associated with increased levels of plaque vulnerability on VH-IVUS images including a higher percentage of NC and a higher prevalence of TCFA [21]. Regarding the findings in the present study, EI and RI in the ACS group were more than those in the SA group on gray-scale IVUS, suggesting that culprit coronary lesion in the ACS group mainly presented with more eccentric plaques and positive vascular remodeling. As previously suggested, plaque composition has impact on vascular remodeling in atherosclerotic coronary arteries [22]. The association of non-culprit coronary lesions in ACS patients with lipid-rich plaques has been confirmed, indicating that plaques instability is extensively developed [23]. Complex coronary plaques in ACS patients may be prone to plaque vulnerability, and positive vascular remodeling in culprit coronary lesion presented association with NC plaque composition on VH-IVUS [24]. In addition, the culprit plaques were mainly differentiated in FT and DC in the SA group, and FF and NC in the ACS, and a characteristic of vulnerable plaque was also observed in the ACS group. It has been documented that more unstable culprit lesions, greater amounts of NC and smaller amounts of fibrofatty plaque are found in ACS patients relative to target lesions in SA patients on VH-IVUS [25]. Non-calcific attenuated plaques assessed on gray-scale IVUS are mainly observed in ACS patients, and are related to a great deal of NC on VH-IVUS and are markers of fibroatheromas

Table 7. IVUS examination results in the intervention group and the non-intervention group for borderline coronary lesions

	Intervention group (n = 17)		*P*	Non-intervention group (n = 69)		*P*
	SA group (n = 6)	ACS group (n = 11)		SA group (n = 32)	ACS group (n = 37)	
PA (mm^2)	7.49 ± 1.13	7.63 ± 1.18	0.827	7.35 ± 1.59	7.52 ± 2.37	0.729
PB (%)	73.41 ± 1.55	78.39 ± 3.82	0.796	66.54 ± 8.86	69.55 ± 11.16	0.466
VAD (mm)	4.13 ± 0.57	4.69 ± 0.48	0.06	3.42 ± 0.27	3.89 ± 0.79	0.038
LAD (mm)	1.56 ± 0.11	1.62 ± 0.15	0.418	1.63 ± 0.46	1.46 ± 0.42	0.021
DSR (%)	61.00 ± 9.23	62.97 ± 7.03	0.646	54.00 ± 4.61	58.89 ± 4.58	0.035
EI	1.12 ± 0.27	1.49 ± 0.33	0.045	1.03 ± 0.30	1.08 ± 0.35	0.524
RI	1.15 ± 0.24	1.41 ± 0.21	0.044	1.08 ± 0.29	1.12 ± 0.38	0.625

Note: IVUS, intravascular ultrasound; ACS, acute coronary syndrome; SA, stable angina; PA, plaque area; PB, plaque burn; VAD, vessel average diameter; LAD, lumen average diameter; DSR, diameter stenosis rate; EI, eccentricity index; RI, remodeling index.

Table 8. Results of IVUS examination in the intervention group and the non-intervention group

	Intervention group (n = 17)		Non-intervention group (n = 65)	
	SA group (n = 6)	ACS group (n = 11)	SA group (n = 30)	ACS group (n = 35)
Recurrent angina	1.00	2.00	3.00	4.00
Revascularization	0.00	0.00	0.00	1.00
Myocardial infarction	0.00	1.00	0.00	1.00
Sudden cardiac death	0.00	0.00	0.00	0.00
Adverse cardiovascular events (n)	1.00	3.00	3.00	5.00

Note: IVUS, intravascular ultrasound; ACS, acute coronary syndrome; SA, stable angina.

occurrence [26]. Currently, pooled evidence indicated that larger areas of DC and NC were in close relation to subsequent coronary events in ACS patients and distal embolization after PCI on VH-IVUS [27, 28].

Another significant finding in our study LDL levels were positively correlated with FF area; HDL level was negatively correlated with FF area and NC area, suggesting that IVUS-VH may guide early interventional therapy for the high-risk patients combined with clinical lipid levels. In the VH-IVUS analysis, patients with a high LDL-C/HDL-C ratio had a larger lipid volume and a smaller fibrous volume, and patients with a high LDL-C/HDL-C ratio have increased risk of cardiovascular events [29]. VH-IVUS detects marked differences in coronary plaque composition related to the risk factor profile with particular focus on lipid levels. Greater amounts of NC were associated with diabetes, hypertension, myocardial infarction (MI), and low HDL-C [30]. Small HDL particles are related to larger PB and more non-calcified plaques, whereas contrary as for larger HDL particles on VH/IVUS [31]. Coronary LDL-C levels correlated with plaque burden along the culprit lesions, and LDL-C may be a good marker for total coronary plaque volume investigated by VH-IVUS [32].

In patients underwent stent implantation, post-operative IVUS showed good stent expansion, no artery dissection or thrombosis. IVUS guided interventional therapy achieved better effect regarding PA, PB, VAD, LAD, DSR, EI and RI, as well as MACE. Favorable outcomes in patients with intermediate coronary artery disease are benefited from both FFR- and IVUS-guided PCI strategy [33]. The NC component on VH-IVUS and plaque morphologic characteristics on gray-scale IVUS are in close relationship to distal embolization phenomenon after PCI [34]. Furthermore, IVUS has a limited role in the functional assessment of angiographically intermediate stenoses, but is a valuable and established tool to guide PCI in assessment of the intermediate coronary stenosis [35]. IVUS-guided appropriate stent or balloon sizing might be useful to prevent post-procedural incomplete stent apposition and optimize initial stent deployment, and IVUS guidance resulted in a comparable degree of stent expansion [36,

37]. It has been suggested that IVUS guidance during DES PCI may result in less stent thrombosis, non peri-procedural MI and cardiac mortality during 1 year follow-up [38]. It is safe for primary and wide use of IVUS to guide PCI and significantly reduced volume of iodine contrast has been found compared to angiography-alone guidance [39]. TCFA identified by VH-IVUS was associated with nonrestenotic and total MACE on individual plaque analysis, and VH-IVUS can identify plaques at increased risk of subsequent events in patients with SA or troponin-positive ACS referred for PCI [40]. In the present study, 2 patients with NC > 20% did not meet the IVUS standard for interventional therapy regarding PA and BD, but the 2 patients were given stent interventional therapy due to poor therapeutic effect and repeated attacks of chest pain, and clinical symptoms are disappeared. Currently, there is no evidence to support the need for prophylactic intervention therapy. However, the positive exploration t is becoming a topic for each interventional physician.

In summary, these preliminary findings revealed that conventional CAG results may underestimate lesion extent in distinguishing ICL, IVUS can further define the extent and nature of the lesions to guide the interventional therapy, and IVUS-VH can improve the diagnosis of vulnerable plaque, characterize plaque composition, and guide early interventional therapy for the high-risk patients combined with clinical lipid levels, particularly for patients without severe vascular stenosis but with significantly increased necrotic component. Future studies are still needed to assess the potential use of this tool for improved patient outcomes.

Acknowledgements

We would like to acknowledge the helpful comments on this paper received from our reviewers.

Disclosure of conflict of interest

None.

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