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Original article

Visualization of coronary plaque in type 2 diabetes mellitus patients using a new 40 MHz intravascular ultrasound imaging system

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KEYWORDS
Angina pectoris;
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Summary
Background: Previous epidemiological studies demonstrated plaque vulnerability to be high in diabetic patients. iMap-intravascular ultrasound (IVUS) is a recently developed radiofrequency 40 MHz IVUS imaging system for tissue characterization. This study aimed to characterize coronary plaque in target lesions of diabetic patients using iMap-IVUS.
Methods: We studied 175 treated vessels in 146 patients with stable angina pectoris and analyzed plaque components of culprit lesions by iMAP-IVUS. Patients were divided into 2 groups: non-diabetic (non-DM: 112 vessels, 93 patients) and diabetic (DM: 63 vessels, 53 patients).
Results: In gray-scale IVUS 2D analysis, there were no differences in IVUS parameters. In 3D analysis, the DM group tended to have a larger plaque volume ($p = 0.07$) and plaque burden ($p = 0.10$). At minimum lumen sites, the absolute lipidic and necrotic areas ($0.84 \pm 0.44\,mm^2$ vs. $0.58 \pm 0.41\,mm^2$, $p < 0.001$, and $2.42 \pm 1.65\,mm^2$ vs. $1.46 \pm 1.76\,mm^2$, $p < 0.001$, respectively) and percent lipidic and necrotic areas were significantly greater in the DM than in the non-DM group ($8.39 \pm 3.38\%$ vs. $5.25 \pm 2.30\%$, $p < 0.0001$, and $23.65 \pm 11.54\%$ vs. $12.99 \pm 10.71\%$, $p < 0.0001$, respectively). In addition, the absolute lipidic and necrotic volumes ($11.75 \pm 10.59\,mm^3$ vs. $8.18 \pm 6.24\,mm^3$, $p < 0.01$, and $29.99 \pm 28.90\,mm^3$ vs. $19.44 \pm 19.35\,mm^3$, $p < 0.01$, respectively) and percent lipidic and necrotic volumes were significantly greater in the DM than in the non-DM group ($6.27 \pm 1.92\%$ vs. $5.13 \pm 1.82\%$, $p < 0.0001$, and $16.54 \pm 7.56\%$ vs. $12.08 \pm 6.05\%$, $p < 0.0001$, respectively).
Conclusion: Characterization of coronary plaque by iMAP-IVUS in diabetic patients showed increased lipidic amount and necrotic plaque volume relative to subjects without DM.

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Introduction

Type 2 diabetes mellitus (DM) is strongly associated with the development of coronary heart disease [1]. Patients with DM also have higher mortality and risk for acute coronary syndrome (ACS) than non-DM patients [2]. Pathological studies showed the main cause of ACS to be rupture of a thin-capped fibroatheroma with a large necrotic core [3]. Previous studies of ACS patients using gray-scale intravascular ultrasound (IVUS) demonstrated that plaque rupture, thrombosis, and vessel remodeling are associated with plaque vulnerability. However, this technique is less accurate in assessing soft tissue components, and has been regarded as a limitation of gray-scale IVUS [4]. Spectral analysis of IVUS which allows detailed assessment of components has been suggested to be more useful for evaluating plaque characteristics than gray-scale IVUS [5]. Recently, several studies employing virtual histology-IVUS (VH-IVUS) (Volcano Therapeutics, Inc., Rancho Cordova, CA, USA) have shown an increased amount of necrotic core in the coronary plaques of type 2 DM patients [6]. While a VH-IVUS system has only 20 MHz in gray-scale resolution, iMap-IVUS (iMap; Boston Scientific Corp, Fremont, CA, USA) is a recently developed IVUS imaging system for tissue characterization with 40 MHz radiofrequency. iMap software converts the signal pattern into a frequency spectrum, and then compares it with spectra obtained from various tissues at autopsy (''data library'') to find the closest match. Since different tissue types (fibrotic, lipidic, necrotic, and calcified) have distinctive spectra, iMap technology can identify tissues from the frequency spectrum that most closely resembles the one obtained by examination [7]. Furthermore, this system provides volumetric analysis. We assessed the coronary plaque characterization in culprit lesions in atherosclerotic vessels of diabetic patients with stable angina pectoris (SAP) using iMAP-IVUS.

Materials and methods

Study population

In this single-center study, a total of 146 patients were selected from 159 consecutive SAP patients. They underwent percutaneous coronary intervention (PCI) and also iMap-IVUS examination between July 2009 and September 2010. SAP was defined as class I or II angina unchanged for more than 2 months or a positive stress test. The target lesion was de-novo (>75% angiographic stenosis by visual estimation) and identified by a combination of left ventricular wall motion abnormalities, electrocardiogram findings, angiographic lesion morphology, and scintigraphic defects. In total, 13 patients were excluded because of 9 in-stent restenosis, 2 visible thrombus with angiography, and 2 inadequate IVUS images. The study population consisted of 146 patients (175 vessels). All patients underwent stent implantation. Type 2 DM was defined as receiving oral hypoglycemic agents, insulin to lower blood glucose levels, known fasting blood glucose values of $\geq$126 mg/dl, and/or postprandial 2-h blood glucose values $\geq$200 mg/dl. Hyperlipidemia was defined as a total cholesterol (TC) level $\geq$220 mg/dl, low-density lipoprotein (LDL) cholesterol $\geq$140 mg/dl, fasting triglycerides (TG) $\geq$150 mg/dl, or medication use. Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of an antihypertensive drug. Estimated glomerular filtration rates (eGFR) were calculated by the modification of diet in renal disease (MDRD): eGFR $(\mathrm{ml/min/1.73\,m^2}) = 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287}$ (Corrected for females by multiplication with a factor of 0.739) [8]. LDL concentration is estimated indirectly from the measured levels of TG, high-density lipoprotein cholesterol (HDL), and TC using the Friedewald equation: LDL (mg/dl) = TC − HDL − (TG/5) [9]. The value for HbA1c (%) was estimated as a National Glycohaemoglobin Standardization Program (NGSP) equivalent value (%), calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society; JDS) (%) + 0.4%. This calculation takes into consideration the relationship between HbA1c (JDS) (%), measured by the previous Japanese standard substance and measurement methods, and HbA1c (NGSP) [10]. Approval to conduct the study was obtained from the ethics committee at our institute, and written informed consent was provided by all participants.

PCI procedure

The patients were pre-medicated with aspirin (100 mg/day) plus clopidogrel (75 mg/day) for at least a week before the procedure. They also received intravenous unfractionated heparin just before PCI to achieve an activated partial thromboplastin time >250 s. None of the patients were given glycoprotein IIb/IIIa inhibitors because these drugs have not been approved in Japan.

IVUS imaging and analysis

IVUS was performed before stenting and after intra-coronary administration of 125—250 μg of nitroglycerin. Data were acquired with a 40 MHz IVUS catheter (Atlantis SR Pro, Boston Scientific). The catheter was advanced beyond the target lesion, and imaging was performed during automatic pullback at a speed of 0.5 mm/s. The IVUS data were stored on a hard disk for off-line analysis, which was performed independently by 2 experienced analysts (T.A. and M.U.) who were unaware of the angiographic findings or the baseline clinical and lesion characteristics. The first observer repeated a blind analysis of all of the data at 2 separate time points (with an interval of at least 1 month between the 2 analyses). Quantitative analysis of gray-scale IVUS images was performed according to the criteria of the American College of Cardiology Clinical Expert Consensus Document on IVUS [11]. Lesions were qualitatively analyzed with iMap software (QIvus 2.0, Medis Medical Imaging Systems bv, Leiden, The Netherlands). The external elastic membrane (EEM) and lumen cross-sectional area (CSA) were measured. Plaque CSA was calculated as EEM minus lumen CSA, and plaque burden was calculated as plaque plus media divided by EEM CSA. The minimum lumen site at the culprit lesion was identified from axial and longitudinal plaques. If there were several slices with equal lumen sizes, the one with the largest EEM and plaque CSA was selected. Lesion length was defined as the segment between distal to proximal reference sites

that appeared normal within 5 mm proximal and distal to the lesion. Proximal and distal references were the single slices with the largest lumen and smallest plaque burden within 5 mm proximally and distally, but before any large side branch.

iMap-IVUS tissue characterization

The iMap-IVUS analysis classified plaque into 4 tissue components and produced color images (green for fibrotic plaque, yellow for lipidic plaque, red for necrotic plaque, and blue for calcified plaque) (Fig. 1). The absolute plaque area (mm^2), plaque volume (mm^3), and percentage of each tissue component were determined. The percent plaque volume was defined as the ratio of plaque volume to EEM volume, and each plaque component was represented as a ratio of the total plaque volume (%fibrotic, %lipidic, %necrotic, and %calcified). The percent plaque area and each component were also defined. Plaque that was unsuitable for analysis was defined as acoustic shadowing area and volume behind calcification or wire artifact and removed automatically because we could not analyze this plaque accurately. The plaque area found to be unsuitable for analysis was $1.22 \pm 0.99\,mm^2$ ($11.84 \pm 8.22\%$) in the DM and $1.23 \pm 1.15\,mm^2$ ($11.65 \pm 9.21\%$) in the non-DM group. The volume unsuitable for analysis was $20.66 \pm 18.92\,mm^3$ ($11.48 \pm 5.59\%$) in the DM and $15.64 \pm 14.01\,mm^3$ ($9.88 \pm 4.92\%$) in the non-DM group.

Statistical analysis

Continuous variables are expressed as the mean $\pm$ standard deviation, while discrete variables are presented as numbers and percentages. Differences in mean values between groups were assessed by the unpaired Student's *t*-test. Categorical data were compared using chi-square statistics or Fisher's exact test. Linear regression analysis was used to evaluate the correlation between intra- and inter-observer variability by using Pearson correlation coefficients. A two-sided *p*-value <0.05 was required for statistical significance. The data were analyzed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

The subjects were divided into 2 groups: a non-diabetic group (non-DM: 112 vessels, 93 patients) and a diabetic group (DM: 63 vessels, 53 patients). Baseline patient characteristics are shown in Table 1. In the DM group, 63.9% ($n = 40$) of patients were treated with oral hypoglycemic agents and 4.3% ($n = 9$) with insulin. There were no significant differences between the 2 groups in age, gender, or traditional coronary risk factors.

Angiographic findings

Coronary angiographic findings are summarized in Table 2. There were no significant differences in diseased vessels and lesion site.

Gray-scale IVUS findings

Gray-scale IVUS data are presented in Table 3. In the 2D analysis, there were no significant differences in IVUS parameters between the 2 groups. However, 3D volumetric analysis revealed that the DM group tended to have larger plaque volumes and percent plaque burdens.

iMAP-IVUS findings

At minimum lumen sites, the absolute lipidic and necrotic areas and the percent lipidic and necrotic areas were significantly greater in the DM than in the non-DM group; conversely, percent fibrotic area was significantly smaller in the DM group (Fig. 2A and B). In addition, the absolute lipidic and necrotic volumes and the percent lipidic and necrotic volumes were significantly greater in the DM than in the non-DM group, while percent fibrotic volume was significantly smaller in the DM group (Fig. 3A and B).

Intra- and inter-observer variability of iMAP-IVUS analysis

Intra-observer variability yielded good concordance for EEM volume, lumen volume, plaque volume, and plaque components by iMAP-IVUS: $r = 0.93$ for EEM, $r = 0.95$ for lumen, $r = 0.94$ for plaque, $r = 0.88$ for the fibrotic component, $r = 0.90$ for the lipidic component, $r = 0.93$ for the necrotic component, and $r = 0.94$ for the calcified component. Inter-observer variability was also acceptable: $r = 0.90$ for EEM, $r = 0.88$ for lumen, $r = 0.88$ for plaque, $r = 0.80$ for the fibrotic component, $r = 0.84$ for the lipidic component, $r = 0.82$ for the necrotic component, and $r = 0.88$ for the calcified component.

Discussion

The main finding of the present study is that stable ischemic heart disease is associated with larger lipidic and necrotic plaques in target vessels in DM than in non-DM patients. Previous studies demonstrated DM to be a leading cause of atherosclerosis and that the incidence of cardiovascular mortality was higher than in the general population [12]. It has been proposed that a large lipid and necrotic core is the one of the markers defining vulnerable plaques prone to rupture and thrombosis [13]. One autopsy study of sudden coronary death patients found inflammation and the necrotic core burden to play a much greater role in the progression of atherosclerosis in DM than in non-DM patients [14]. Furthermore, previous ex vivo studies showed DM patients to have more lipid-rich content and macrophage infiltration of coronary atherectomy specimens [15]. These results suggest that patients with DM are at greater risk of developing vulnerable plaque associated with

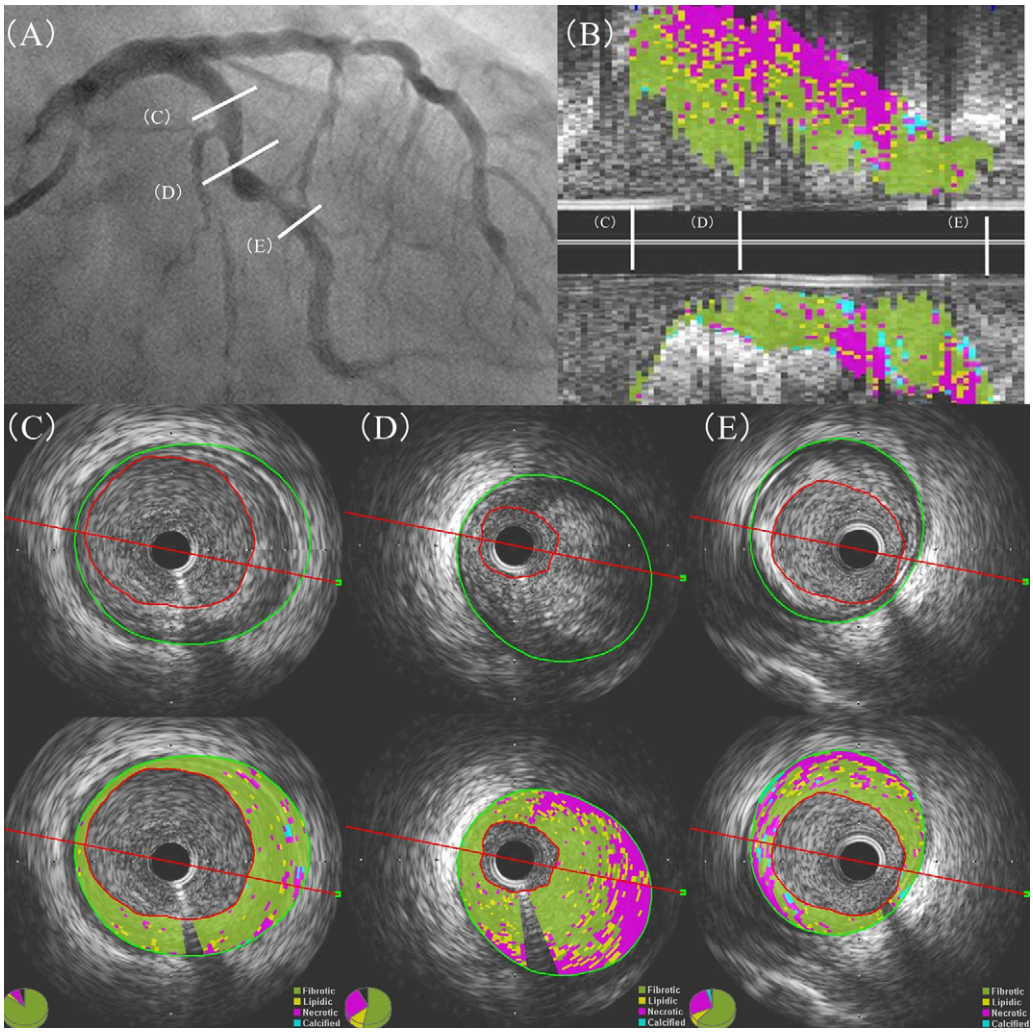

Figure 1 Plaque characterization using gray-scale intravascular ultrasound (IVUS) and iMAP. (A) Coronary angiography (CAG) revealed 90% stenosis in the middle left circumflex artery. (B) Longitudinal imaging of culprit lesion using iMAP-IVUS. (C)—(E) Four cross-sectional gray-scale IVUS (upper panels) and iMAP-IVUS (lower panels) images from proximal (C) to distal (E) within a culprit lesion. (D) The minimum lumen site. iMAP-IVUS demonstrate green for fibrotic plaque, yellow for lipidic plaque, red for necrotic plaque, and blue for calcified plaque. External elastic membrane area, lumen area, and plaque area were 18.61 mm^2, 2.87 mm^2, and 15.74 mm^2, respectively, in (D). The fibrotic, lipidic, necrotic, and calcified areas were 8.47 mm^2 (53%), 1.73 mm^2 (10%), 4.51 mm^2 (28%), and 0.02 mm^2 (0%), respectively, in (D). External elastic membrane volume, lumen volume, and plaque volume are 545.49 mm^3, 151.40 mm^3, and 394.10 mm^3, respectively. The fibrotic, lipidic, necrotic, and calcified areas were 231.12 mm^3 (58%), 30.47 mm^3 (7%), 106.08 mm^3 (26%), and 9.11 mm^3 (2%), respectively.

acute coronary events. A human study using VH-IVUS demonstrated similar findings in stable angina pectoris patients [6]. Also, in integrated backscatter (IB)-IVUS analyzed plaque component using IB value, lipid area and volume in hyperinsulinemia and lipid core in DM is larger than non-DM [16,17]. The results of this report appear to be consistent with our data showing DM patients to have large lipidic and necrotic plaques at culprit lesion sites. It is noteworthy that differences in plaque characteristics were observed despite both groups of patients having stable ischemic heart disease. Furthermore, previous studies demonstrated culprit lesions in DM patients to be characterized by negative remodeling, a larger plaque burden, and more diffuse disease [18]. We detected no difference in vessel volume between DM and non-DM patients, though plaque volume tended to be greater in the DM group. These findings suggest that adaptation via coronary remodeling is minimal in diabetic patients, an observation apparently consistent with those of previous studies [19]. DM patients have diffuse atherosclerosis and a large plaque burden. Therefore, it seems reasonable that tissue characterization by volumetric analysis yields more information than a 2D image.

iMAP-IVUS not only allows online delineation of tissue components for each category, but also provides real-time 40 MHz high-resolution gray-scale images, which are also fundamentally important. Most previous intra-coronary tissue classification studies employed VH-IVUS, in which gray-scale resolution is only 20 MHz [6,20—23]. 2D analysis has the same limitation. After the aforementioned studies, VH-IVUS was introduced in clinical settings and then

Table 1 Baseline characteristics.

	Non-DM ($n=112$)	DM ($n=63$)	p-Value
Age (years)	69.6 ± 9.9	68.03 ± 12.4	0.87
Male gender (%)	94 (83.9)	49 (79.1)	0.41
Smoking (%)	50(44.6)	34 (54.0)	0.30
Prior MI (%)	14 (12.5)	5 (7.9)	0.50
Prior CABG (%)	5 (4.5)	1 (1.6)	0.57
Family history (%)	14 (12.5)	6 (9.5)	0.73
Ejection fraction (%)	60.81 ± 12.77	59.15 ± 13.71	0.43
Hypertension (%)	89 (79.5)	56 (88.9)	0.17
Hyperlipidemia (%)	69 (61.6)	45 (71.4)	0.25
Hemodialysis (%)	11 (9.8)	8 (12.7)	0.73
eGFR (ml/min/1.73 m^2)	45.15 ± 18.29	42.89 ± 26.12	0.50
Fasting blood glucose (mg/dl)	107.72 ± 25.01	143.43 ± 47.26	<0.0001
Hemoglobin A1C (%)	5.83 ± 0.32	7.01 ± 1.17	<0.0001
Total cholesterol (mg/dl)	173.52 ± 41.15	170.62 ± 32.59	0.63
Triglyceride (mg/dl)	134.83 ± 116.04 (71.1—140.9)[a]	122.35 ± 58.00 (67.5—158.5)[a]	0.43
LDL-cholesterol (mg/dl)	97.22 ± 34.07	97.61 ± 28.43	0.94
HDL-cholesterol (mg/dl)	51.12 ± 14.77	48.27 ± 10.73	0.19
Statin use (%)	68 (60.7)	43 (68.3)	0.41
ACE-I or ARB use (%)	58 (51.8)	44 (69.8)	0.09
Oral hypoglycemic agents (%)		40 (63.9)	
Insulin user (%)		9 (14.3)	

Data are presented as the number (%) of patients or means ± SD.
DM, diabetes mellitus; MI, myocardial infarction; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.
[a] Interquartile range.

widely used, although disagreements persist regarding its accuracy [24,25]. In iMAP-IVUS, further prospective studies are required to validate our findings and confirm the usefulness of this new modality, which may provide more in depth information about tissues [26,27].

Limitations

First, this was a single center, retrospective study. Selection bias cannot be entirely avoided. Second, we excluded patients with restenosis after stent implantation and inadequate IVUS images. Therefore, this study might not represent the entire spectrum of patients with angina pectoris. Third, the present iMAP-IVUS modality is unable to differentiate thrombus from other plaque components. Although we excluded angiographically detected thrombus, a small thrombus within plaque CSA might lead to incorrect tissue characterization. In a future study, it will be necessary to develop an iMAP-IVUS algorithm for thrombus. Fourth, some areas of plaque were unsuitable for analysis due to calcification and guide-wire artifacts. Fifth, while nitroglycerin was administered before IVUS imaging, the occurrence

Table 2 Coronary angiographic findings.

	Non-DM ($n=112$)	DM ($n=63$)	p-Value
Diseased vessel (%)			0.85
Left main	4 (3.6)	4 (6.3)	
Left anterior descending	46 (41.1)	24 (38.1)	
Left circumflex	22 (19.6)	13 (20.6)	
Right	40 (35.7)	22 (34.9)	
Lesion site (%)			0.87
Proximal	54 (48.2)	28 (44.4)	
Middle	41 (36.6)	24 (38.1)	
Distal	17 (15.2)	11 (17.5)	

Data are presented as the number (%) of patients.
DM, diabetes mellitus.

Table 3 Gray-scale intravascular ultrasound findings.

	Non-DM ($n = 112$)	DM ($n = 63$)	p-Value
Gray-scale IVUS analysis (2D)			
External elastic membrane area (mm^2)	12.75 ± 4.40	12.59 ± 4.08	0.82
Lumen area (mm^2)	3.11 ± 1.24	2.87 ± 0.89	0.19
Plaque area (mm^2)	9.64 ± 3.77	9.73 ± 3.83	0.88
Plaque burden (%)	74.72 ± 7.98	75.58 ± 8.89	0.52
Gray-scale IVUS analysis (3D)			
External elastic membrane volume (mm^3)	193.49 ± 115.08	225.04 ± 148.82	0.12
Lumen volume (mm^3)	55.65 ± 36.88	59.53 ± 37.06	0.51
Plaque volume (mm^3)	136.44 ± 88.53	165.51 ± 120.39	0.07
Plaque burden (%)	68.4 ± 11.6	71.3 ± 10.5	0.10
Lesion length (mm)	16.06 ± 7.77	18.04 ± 8.48	0.12

Data are presented as means ± SD.
DM, diabetes mellitus; IVUS, intravascular ultrasound.

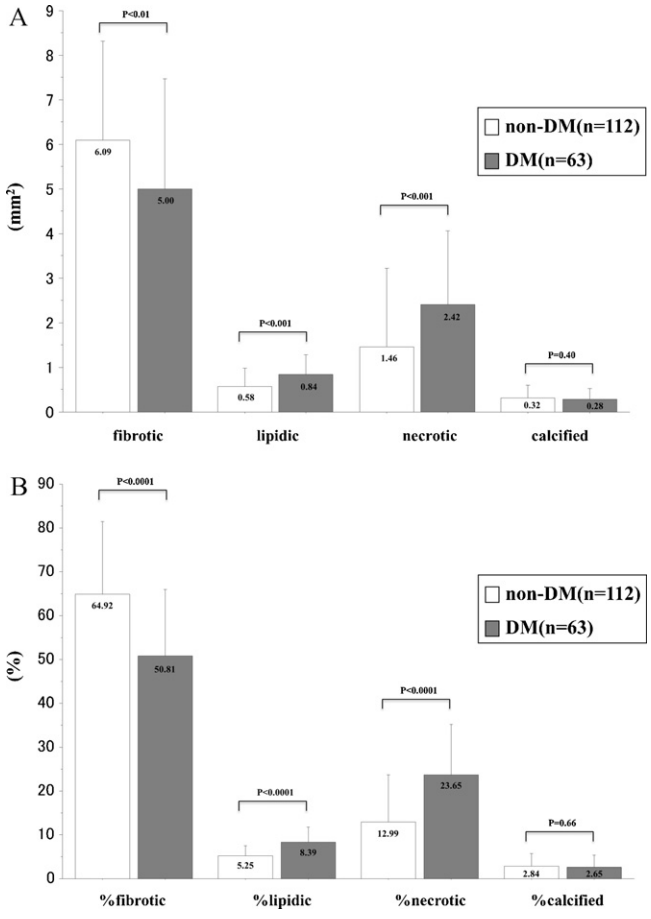

Figure 2 Absolute and relative plaque areas at minimum lumen sites. The absolute (A) and relative (B) areas at minimum lumen sites in a subset of 175 vessels undergoing iMAP-intravascular ultrasound (IVUS) are shown. The absolute lipidic and necrotic areas and percent lipidic and necrotic areas were significantly greater in the diabetes mellitus (DM) than in the non-DM group; conversely, the percent fibrotic area was significantly smaller in DM group.

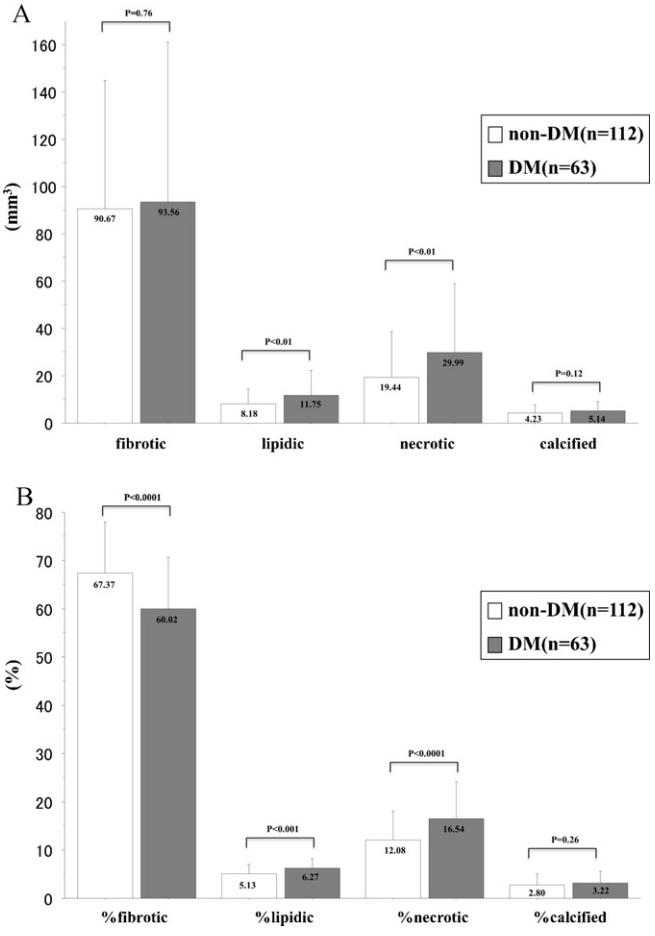

Figure 3 Volumetric absolute and relative plaque components. Volumetric absolute (A) and relative (B) plaque components in a subset of 175 vessels undergoing iMAP-intravascular ultrasound (IVUS) are shown. The absolute lipidic and necrotic volumes and percent lipidic and necrotic volumes were significantly greater in the diabetes mellitus (DM) than in the non-DM group; conversely, the percent fibrotic volume was significantly smaller in the DM group.

of vasospasm cannot be completely ruled out. Sixth, only vessels undergoing PCI were examined. Finally, the culprit lesions analyzed constituted only a small part of the entire coronary arterial system.

Conclusion

iMAP-IVUS revealed that DM patients have significantly larger lipidic and necrotic plaque volumes than non-DM patients.

Conflicts of interest

None.

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