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Original

Comparison of microvessel visualization using optical coherence tomography and lesion characteristics in coronary artery disease: clinical implications

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Abstract

The purpose of this study was to evaluate the clinical significance of visualizing microvessels (MV) using optical coherence tomography (OCT) in patients with chronic coronary artery disease. A total of 96 consecutive patients who underwent OCT prior to elective percutaneous coronary intervention (PCI) were evaluated. Patients were divided into the MV group (53 patients) and the non-MV group (43 patients). We compared patient and lesion characteristics between the two groups. There was significant difference in calcification (p=0.041) and the length of macrophage image (p=0.045), and differences slightly below the significance threshold in age (p=0.064), the logarithmic HDL-choresterol level (p=0.067), plaque erosion (p=0.059), lipid cap thickness (p=0.074) and the macrophage grade (p=0.056). Moreover, age (odds ratio 0.943, 95%CI 0.893-0.997, p=0.039), logarithm of HDL-C (odds ratio 0.010, 95%CI 0.000-0.919, p=0.046), and length of macrophage image (odds ratio 1.290, 95%CI 1.019-1.633, p=0.035) were independent variables predictive of the presence of microvessels. Our results suggest that the existence of MV near coronary plaque is associated with younger age, lower HDL-C levels and advanced coronary plaque. The presence of MV correlates with coronary plaque ageing and vulnerability in patients with chronic coronary artery disease.

Key words : *optical coherence tomography, microvessel, stable coronary artery disease, vulnerable plaque*

I. Introduction

The origin and progression of coronary atherosclerosis was initially thought to be based on Ross's response to injury hypothesis [1]. Recently, however, mechanisms of atherosclerosis have been analysed using advanced molecular biology techniques [2]. Specifically, the mechanism of plaque rupture has been analysed in patients with acute coronary syndrome caused by plaque disruption and mild atherosclerosis [3]. The main cause of acute coronary syndrome (ACS) onset was thought to include plaque rupture due to the presence of thin cap fibroatheromas (TCFA) and matrix metalloproteinase (MMP) [4-6].

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A previous study reported that microvessel (MV) growth occurred in the adventitia of the blood vessel with an arteriosclerosis lesion. It was reported that MV mainly came from the adventitial vasa vasorum and invaded the neointima through a media from the adventitia side of the blood vessel, and that these vessels played a role in the transportation pathway to the coronary plaque. This transportation pathway at the sites of atherosclerosis supplies inflammatory cells, red cells and membrane lipids. When MV invade a lesion, they meld with the extracellular matrix. It is thought that the plaque is destabilized by mechanisms such as these that compromise the structure of the plaque [7-10]. Moreover, these mechanisms result in stable plaques becoming unstable plaques [1, 11]. Thus, de novo vessels readily produce intra-plaque bleeding and cause plaque disruption [12, 13]. On the other hand, intra-plaque MV are thought to be a repair response to injured intima (i.e., a restorative response to inflammation) [14].

A previous study reported on evaluation of MV visualized by OCT in patients with chronic and acute coronary syndrome [15]. However, there have been no reports evaluating the clinical implications of MV in patients with only stable coronary artery disease. The purpose of this study was to evaluate the clinical significance of visualizing MV using optical coherence tomography (OCT) in Japanese patients with chronic coronary artery disease.

II. Materials and methods

1. Study Patients

The subjects were selected from 1,233 consecutive patients who underwent elective PCI at our institution between October 2011 and July 2015. Of these patients, 96 consecutive patients analysed using OCT just before PCI were evaluated. When there were two lesions in a case, we analysed the lesion with the higher stenosis rate in the blood vessel. Exclusion criteria were as follows: patients with prior myocardial infarction who had an infarct in a related artery (two cases), patients in whom the OCT image was acquired after basic balloon angioplasty, and patients with poor OCT images that were too difficult to analyse (nine cases). Patients were divided into two groups: the MV group and the non-MV group. We compared patient and lesion characteristics between the two groups. This study was approved by the ethics committee at our institution.

2. OCT image acquisition

We performed OCT according to Judkin's technique via the trans-radial approach using a 6-French system. The ILLUMIEN OPTIS™ imaging system with the Dragonfly-JP™ imaging catheter (St. Jude Medical, St. Paul, MN, USA) was used. After the insertion of a 0.36 mm intervention guide wire, the imaging catheter was carefully advanced distally to the target lesion under fluoroscopic guidance. Contrast medium was flushed continuously through the guiding catheter during image acquisition, and motorized pullback OCT imaging was performed at a pullback rate of 18 mm/sec (HD mode) or 36 mm/sec (S mode) throughout the whole lesion.

3. OCT image analysis

OCT analysis was performed using LightLab OCT imaging proprietary software (LightLab Imaging/St. Jude Medical, Westford, MA, USA) by two experienced observers

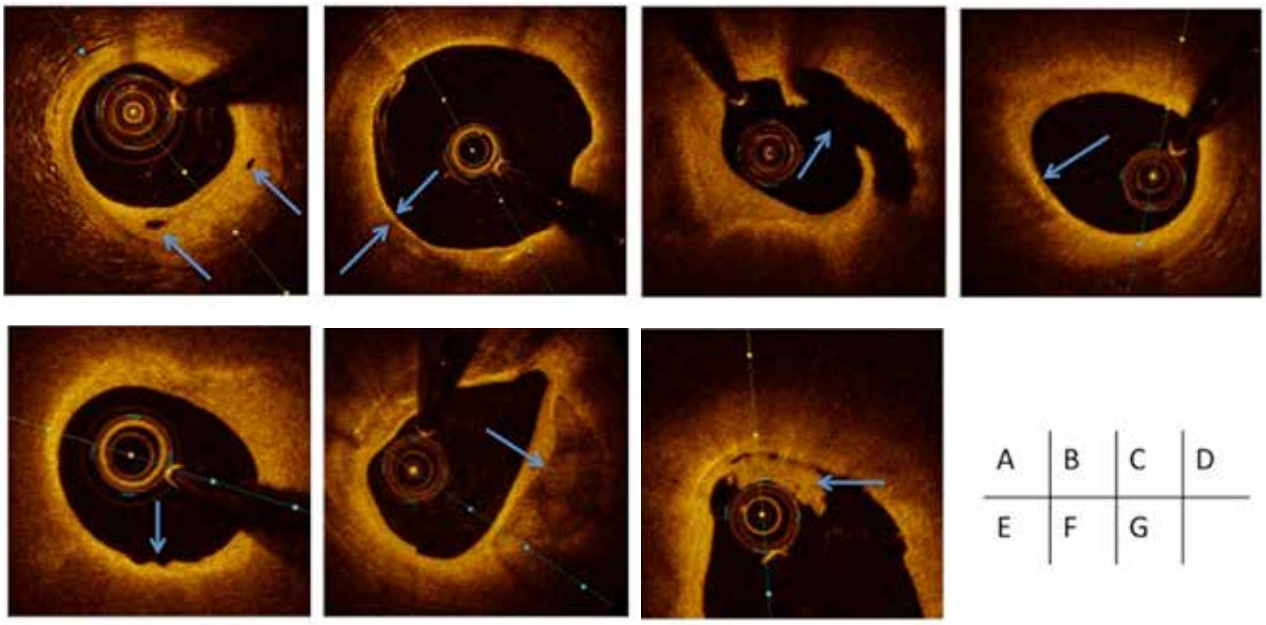

Fig. 1. OCT image.
microvessel (A), thin cap fibro–atheroma (B), plaque rupture (C), macrophage (D), erosion (E), calcium deposition (F), thrombus (G)

independent of PCI. Images were evaluated and interpreted by discussion between two experienced observers. The target lesion was defined using a stent landing segment with a 5 mm addition to both proximal and distal sides. The stent area was identified in reference to a lateral branch and calcification on the OCT image after the stent placement. Patients were divided into two groups: those with and those without MV analysis. MV were defined according to criteria outlined in previous reports [15,16]; namely, a microchannel was defined as a 'no-signal tubulo-luminal structure with and without a connection to the vessel lumen' if observed on ≧3 consecutive cross-sectional OCT images and if its diameter was between 50 and 150 μm (Fig. 1A). The minimal lumen area was automatically measured using proprietary imaging software and manually corrected by an experienced observer.

The assessment of tissue properties was performed according to a previous report and consensus [16-18]. The lipid pool was defined as homogenous, diffusely bordered, signal-poor regions. Lipid cap thickness was defined as the thickness of the fibrous cap covering the lipid pool. Thin cap fibroatheromas (TCFA) were defined as having a thin cap thickness of < 65 μ m (Fig. 1B). Plaque rupture was defined as a disrupted fibrous membrane with an underlying empty cavity (Fig. 1C). Intimal laceration was defined as the irregularity or disruption of the superficial intimal lining without fibrous cap rupture. Maximum lipid angle, maximum calcium angle, and maximum macrophage angle were measured in a target lesion around a point of intersection of the largest and smallest diameter of the blood vessel lumen. Macrophage accumulation was defined as a high-intensity, signal-rich linear region with sharp attenuation (Fig. 1D).

Macrophage grade was defined according to previous reports, and macrophages were classified into five groups [19,20]. Macrophage signals were semi-quantitatively graded as follows: grade 0, no macrophages; grade 1, localized macrophage accumulation; grade 2, clustered accumulation in <1 quadrant; grade 3, clustered accumulation in >1 quadrant but <3 quadrants; and grade 4, clustered accumulation in >3 quadrants. To distinguish between grade 1 and 2, the degree of macrophage extension was defined as 30 degrees. Total macrophage grade was defined as the summation of macrophage grades in each cross section every 1 mm from the maximum macrophage arc frame to the disappearance of the macrophage frame. Plaque erosion was defined according to OCT erosion categories described in a previous report [17], i.e., according to the absence of fibrous cap disruption and the presence of thrombus. Definite OCT erosion was defined as the presence of an attached thrombus overlying an intact and visible plaque. Probable OCT erosion was defined as: 1) luminal surface irregularity at the target lesion in the absence of thrombus, or 2) attenuation of an underlying plaque by a thrombus without superficial lipid or calcification immediately proximal or distal to the thrombus (Fig. 1E). Calcification was defined as a signal-poor or heterogeneous region with a sharply delineated border (leading, trailing, and/or lateral edges) (Fig. 1F). Thrombus was also defined as protruding masses attached to the lumen wall (Fig. 1G).

4. Quantitative coronary angiography

The target lesion was analysed using quantitative coronary angiography on a QCA-CMS system, version 7.1 (Medis Medical Imaging Systems, Leiden, The Netherlands) using the external diameter of the contrast-filled guiding catheter as the calibration standard. Minimal lumen area, lesion length, % diameter stenosis, and reference diameter were measured by QCA-CMS. Percent diameter stenosis was calculated from the minimal lumen diameter and the reference diameter.

5. Statistical analysis

Data are presented as the mean ± SD. The frequency between the 2 groups was assessed using the chi-square test. Non-normally distributed data were identified using the Mann–Whitney U test. Normally distributed data, after logarithmic transformation, was analysed using the unpaired t-test. Macrophage grade was assessed using the Kolmogorov-Smirnov test because the form of the distribution was different. For multivariate analysis, we examined variables with clause 2 logistic regression analysis, using the item with a significant difference or the tendency in the clinical factor and the OCT image. Differences were considered significant at $p<0.05$. All statistical analyses were performed using SPSS Ver. 22 for Windows (Chicago, IL, USA).

III. Results

Baseline clinical and lesion characteristics are shown in Tables 1 and 2. Target plaque characteristics are shown in Table 3. The MV group included 53 lesions, and the non-MV group included 43 lesions. Age in the MV group was lower than that in the non-MV group (66.3 ± 10.7 vs. 70.1 ± 9.3 year-old; $p=0.064$). There were no significant

Table 1. Baseline clinical characteristics of study patients

	MV group (n=53)	non-MV group (n=43)	P value
Age (years)	66.3 ± 10.7	70.1 ± 9.3	0.064
Sex (male/female)	45/8	33/10	0.308
Body mass index (kg/m^2)	25.6 ± 3.7	24.5 ± 3.5	0.142
Hypertension	45 (85%)	38 (88%)	0.622
Diabetes mellitus	16 (30%)	18 (42%)	0.234
Dyslipidemia	39 (74%)	29 (67%)	0.51
PAD	1 (2%)	4 (9%)	0.104
CVD	2 (4%)	2 (5%)	0.831
Prior MI	18 (34%)	17 (40%)	0.573
Prior PCI	27 (51%)	24 (56%)	0.634
Prior CABG	1 (2%)	1 (2%)	0.881
Smoking	11 (21%)	7 (16%)	0.576
HbA1c (%)	6.2 ± 1.0	6.3 ± 0.9	0.378
LDL − C (mg/dL)	99.5 ± 34.3	99.5 ± 35.1	0.794
HDL − C (mg/dL)	47.8 ± 11.2	53.0 ± 14.6	0.17
log HDL-C	1.67 ± 0.11	1.71 ± 0.11	0.067
L/H	2.2 ± 0.9	2.0 ± 0.9	0.441
CRE (mg/dL)	0.8 ± 0.2	0.9 ± 1.0	0.629
eGFR<60 (ml/min/1.73㎡)	10 (19%)	7 (16%)	0.741
eGFR (ml/min/1.73㎡)	79.7 ± 27.3	77.6 ± 23.9	0.854
CRP (<0.1/0.1～0.2/>0.2mg/dL)	30/8/5	31/2/10	0.164
Diseased vessel single/double/triple	25/19/9	20/17/6	0.892
Prescription after index PCI			
Aspirin (%)	53 (100%)	43 (100%)	N/A
ACE/ARB (%)	38 (72%)	33 (77%)	0.575
Statin (%)	42 (79%)	31 (72%)	0.414
Nitrate (%)	17 (32%)	12 (28%)	0.658
Nicorandil (%)	33 (62%)	31 (72%)	0.31
CCB (%)	23 (43%)	18 (42%)	0.88
Beta blocker (%)	28 (53%)	9 (21%)	0.001
Thienopyridine (%)	48 (91%)	42 (98%)	0.152
Coumadin (%)	1 (2%)	2 (5%)	0.439

PAD: peripheral artery disease, CVD: cerebrovascular disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary arterial bypass graft, L/H: LDL-cholesterol/HDL-cholesterol, CRE: creatinine, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, ACE: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker

Table 2. Baseline lesion characteristics

	MV group (n=53)	non-MV group (n=43)	P value
Baseline at index PCI			
Target lesion			
LAD/RCA/LCx	39/10/4	27/11/5	0.519
ACC/AHA			
Classification A/B1/B2/C	5/6/19/23	3/1/21/18	0.286
QCA			
MLD (mm)	0.6 ± 0.3	0.5 ± 0.2	0.208
Lesion length (mm)	18.6 ± 10.5	16.1 ± 7.7	0.225
%DS (%)	75.5 ± 8.5	78.6 ± 5.5	0.507
Reference diameter (mm)	2.5 ± 0.6	2.5 ± 0.6	0.573

LAD: left anterior descending artery, RCA: right coronary artery, LCx: left circumflex artery, QCA: quantitative coronary angiography, MLD: minimal lumen diameter, %DS: % diameter stenosis

Table 3. Quantitative and qualitative OCT findings in the study patients

	MV group (n=53)	non-MV group (n=43)	P value
OCT findings			
In-lesion thrombus	25 (47%)	15 (35%)	0.225
TCFA	4 (8%)	1 (2%)	0.252
Plaque rupture	11 (21%)	9 (21%)	0.983
Lipid pool	52 (98%)	43 (100%)	0.365
Calcium deposition	46 (87%)	30 (70%)	0.041
Macrophage image	51 (96%)	39 (91%)	0.266
Erosion	22 (42%)	10 (23%)	0.059
Intimal laceration	1 (2%)	3 (7%)	0.215
MLA (mm^2)	1.5 ± 0.7	1.4 ± 0.6	0.526
Maximum lipid angle (°)	239.6 ± 95.2	227.7 ± 84.0	0.403
Maximum calc angle (°)	121.4 ± 94.3	106.7 ± 101.2	0.464
Maximum macrophage angle (°)	121.8 ± 79.0	114.9 ± 62.1	0.921
Macrophage length (mm)	3.3 ± 4.0	1.6 ± 1.5	0.045
Macrophage grade	8.6 ± 10.4	4.4 ± 3.5	0.056
Lipid cap thickness (μm)	115.8 ± 78.9	126.5 ± 53.1	0.074

TCFA: thin cap fibro-atheroma, MLA: minimal lumen area

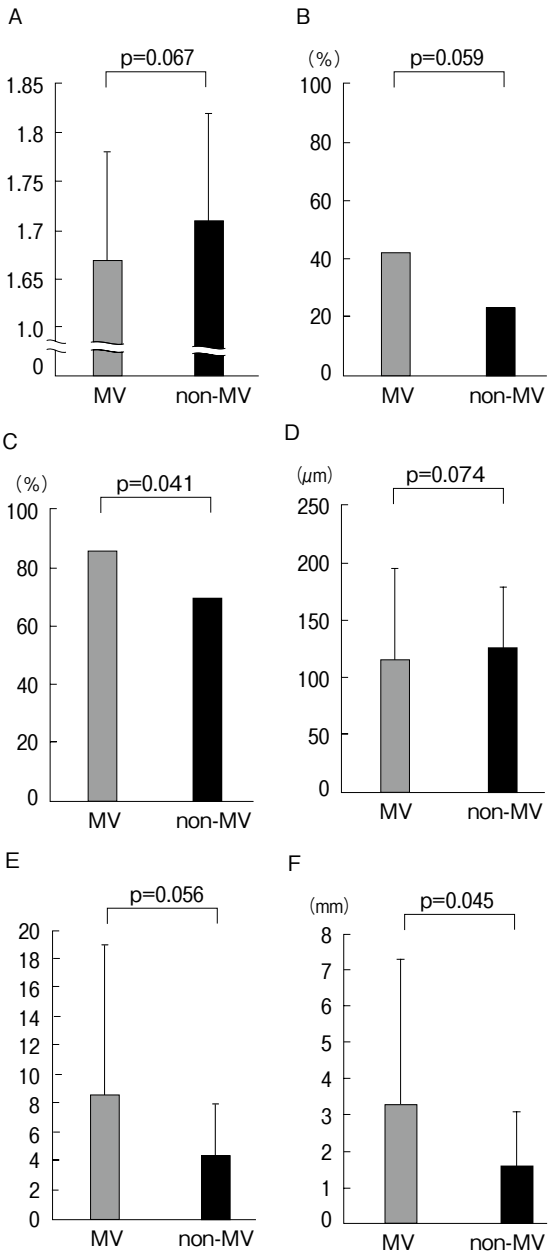

Fig. 2. Comparison of log-HDL cholesterol (A), plaque erosion (B), calcium deposition (C), lipid cap thickness (D), macrophage grade (E) and macrophage length (F) between the groups.

differences between the groups for LDL-C and HDL-C levels, but logarithmic HDL-C levels in the MV group were higher than those in the non-MV group (1.67 ± 0.11 vs. 1.71 ± 0.11; p=0.067) (Fig. 2A). The prevalence of plaque erosion (42 % vs. 23 %) and calcification (87 % vs. 70 %) in the MV group was higher than that in the non-MV group (p=0.059, p=0.041, respectively) (Fig. 2B, 2C). Lipid cap thickness in the MV group was thinner than in the non-MV group (115.8 ± 78.9 μm vs. 126.5 ± 53.1 μm: p=0.074) (Fig. 2D). Although the arc of macrophages was even between the two groups (121.8 ± 79.0° vs. 114.9 ± 62.1°; p=0.921), there was a difference in macrophage grade (8.6 ± 10.4 vs. 4.4 ± 3.5; p=0.056) and a significant difference in the length of the macrophage image (3.3 ± 4.0 mm vs. 1.6 ± 1.5 mm; p=0.045) (Fig. 2E, 2F). Moreover, multivariate regression analysis demonstrated that age (odds ratio 0.943, 95% CI 0.893-0.997, p=0.39), logarithm of HDL-C (odds ratio 0.010, 95%CI 0.000-0.919, p=0.046), and length of macrophage image (odds ratio 1.290, 95%CI 1.019-1.633, p=0.035) were independent OCT-micro vessel predictive factors.

There were no no-reflows or perioperative period myocardial infarctions immediately after PCI in either group.

IV. Discussion

In this study, we evaluated patient characteristics and MV visualized by OCT in patients with chronic coronary disease. The patients in the MV group were younger, and the logarithmic HDL-C level was lower than that of the patients in the non-MV group. Moreover, in terms of lesion characteristics, the length of macrophages, and calcium deposition in the MV group were significantly longer and higher than those in the non-MV group. Macrophage grade and plaque OCT erosion in the MV group was nearly

significantly higher than that in the non-MV group. These factors were identified as independent predictors using logistic regression analysis. These data showing the existence of MV suggested that the plaque had already advanced in spite of the young age of the patients.

Kitabata et al. reported the presence of many lipid plaques, a thin fibrous cap thickness, a higher prevalence of TCFA and a higher sensitivity to CRP levels in the micro channel group than in the non-micro channel group in patients with unstable angina and symptomatic stable angina [15]. There was a positive correlation between the number of micro channels and TCFA. In our study, although fibrous cap thickness was nearly significantly thinner in the MV group than in the non-MV group same as their report, there were no significant differences in the other factors.

We suggest that the cause of this difference is the exclusion of acute coronary syndrome patients and our focus on stable coronary artery disease patients in our study. In our study, the prevalence of calcification in the MV group was higher than that in the non-MV group. Calcification was thought to be a long-term lesion and was regarded as an end stage of the plaque. These findings were thought to indicate that the plaque was highly advanced.

Kato et al. reported that a longer and larger arc for lipid pool, prevalence of TCFA macrophage thrombus and micro–channels in non-target lesions were significantly higher in patients with ACS than in patients without ACS [21]. These results suggest that non-target lesion vulnerability in ACS patients is higher than that in non ACS patients.

Naghavi et al. reported that the cause of acute coronary syndrome is 70% plaque rupture and 30% a combination of plaque erosion and calcified plaque [22]. Jia et al. report that the cause of acute coronary syndrome is 44% plaque rupture, 31% erosion and 8% calcified lesion [17]. Our results suggest that evaluated, stable coronary artery disease has half the number of micro channels, that the length of macrophages in the MV group was significantly longer than in the non-MV group, and that macrophage grade in the MV group was nearly significantly higher than in the non-MV group. Even plaque erosion and calcified lesions associated with plaque vulnerability and our finding that calcified lesions and erosion occur more frequently in the MV group than in the non-MV group was similar to previously published results. These results suggest that even stable coronary artery disease exhibits coronary vulnerability.

Sluimer et al. reported that MV density was increased in advanced plaques compared to early plaques. They reported that plaque MV had thin vessel walls and showed abnormal endothelial cell morphology and aberrant junctions. These characteristics explain the possibility of micro vascular leakage and intraplaque haemorrhage [23].

In our study, MV revealed the severe progression of atherosclerosis and the vulnerability of the patients. These findings do not appear to contradict previous reports.

A previous prospective cohort study reported that low HDL-C levels were elevated in individuals who had experienced cardiovascular events and that this was an independent predictive factor. Another large

scale prospective cohort study reported that it is not LDL-C levels, but low HDL-C levels, that are associated with cardiovascular events in the Japanese population and that low HDL-C levels are a significant predictive factor in the general population [24]. Although our results show no significant differences in HDL-C levels between the groups, the log HDL-C level in the MV group was nevertheless lower than in the non-MV group. Several studies report that low HDL-C levels increase the risk of cardiovascular events in stable coronary artery disease [25]. The findings in these reports appear to be consistent with the results of our study. Previous studies reported that the presence of MV may be associated with the progression and vulnerability of plaques in acute versus stable coronary artery disease. In stable coronary artery disease, the presence of MV may be associated with cardiovascular events and low HDL-C levels may be associated with the presence of MV. Moreover, not only HDL-C levels but also the logarithm of HDL-C levels may predict plaque vulnerability in patients with stable coronary artery disease.

There are several limitations to this study. First, a prognostic evaluation was absent. A further study is needed to determine the prognostic value of this technique by dividing the cohort into groups according to the presence or absence of vulnerable plaques after plaque assessment using OCT. Second, our study was composed of a relatively small number of patients. A multicentre, large number registry is needed for further studies. Third, quantitative evaluation of MV was not performed. Moreover, OCT penetration depth for MV was limited. The OCT determination of whether a MV was true vasa vasorum or adventitia was inconclusive. An additional study is needed to improve the quantitative analysis and to determine if MV are true vasa vasorum, using new and advanced OCT systems with high penetration depth.

Our results suggest that the existence of MV near the coronary plaque is associated with younger age, lower HDL-C levels and progressed coronary plaque. The presence of MV correlates with coronary plaque ageing and vulnerability in patients with chronic coronary artery disease.

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Conflicts of interest: The authors have no conflict of interest to declare.

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光干渉断層法で観察された microvessel と冠動脈病変との比較

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要旨

慢性冠動脈疾患患者で，光干渉断層法 (OCT) で描出される microvessel (MV) の臨床的意義を明らかにする. 待機的 PCI 実施前に OCT を施行した連続 96 名を，MV 群 (53 名) と非 MV 群 (43 名) に分類し，患者背景および OCT 所見を比較検討した．MV 群で，石灰化 , びらんは多く (p=0.041，p=0.059)，マクロファージ長は長く (p=0.045)，年齢，log HDL-C は低く (p=0.064, p=0.067)，脂質被膜厚は薄く (p=0.074)，マクロファージグレードは高かった (p=0.056)．多変量解析では，若年 (odds 比 0.943，95%CI 0.893–0.997，p=0.039)，低 log HDL–C (odd 比 0.01，95%CI 0.000–0.919，p=0.046)，マクとファージ長が長いこと (odds 比 1.29，95%CI 1.019–1.633，p=0.035) が MV の 独立した予測因子であった．冠動脈プラーク近傍での MV の存在は，年齢，低 log HDL-C や進展した冠動脈プラークに関連している可能性が示唆された．MV の存在は，冠動脈プラークの進展や不安定性に関与していた.