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ORIGINAL ARTICLE

Incidence and clinical impact of thrombus after stent implantation in patients with ST-segment elevation myocardial infarction: an optical coherence tomography study

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Abstract

Background: We previously reported that ST-segment elevation myocardial infarction (STEMI) patients with large residual thrombus burden after thrombectomy before stent implantation had more severe microvascular dysfunction, and greater myocardial damage compared with those with small residual thrombus. However, clinical significance of residual thrombus after stent implantation in STEMI patients is unclear.

Aims: This study aimed to evaluate the incidence of thrombus by optical coherence tomography (OCT) after stent implantation, and to investigate its clinical impact in STEMI patients.

Methods and Results: A total of 180 STEMI patients within 12 hours after onset of symptoms were studied. Patients were divided into two groups according to OCT findings after stent implantation: thrombus group (n = 73) and non-thrombus group (n = 107). Peak CPK levels were greater in thrombus group than in non-thrombus group with close to significance (3649 {1752-7053} versus. 2563 {1201-4282} IU/L, p = 0.053). Thrombus after stent implantation was independently associated with peak CPK levels by a stepwise multivariate analysis.

Conclusions: Residual thrombus on OCT after stent implantation was detected in 41% of STEMI patients. The residual thrombus was associated with greater myocardial damage assessed by peak CPK levels, indicating clinical impact of OCT-detected thrombus in STEMI patients.

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Key words: Thrombus; Optical coherence tomography; Coronary artery disease; ST-segment elevation myocardial infarction.

Introduction

The use of an imaging device along with percutaneous coronary intervention (PCI) is a standard therapy for patients with acute coronary syndrome (ACS) and stable angina pectoris (SAP)[1–3)]. Intravascular ultrasound (IVUS) guidance during PCI is useful for improving clinical outcomes[4, 5)]. Optical coherence tomography (OCT) is a recently developed imaging modality that provides intracoronary images with higher resolutions compared with IVUS, and therefore, it's use has been increasing[6)]. However, there is an ongoing debate about the clinical significance of post-stenting OCT findings.

In the previous studies, large thrombus burden on angiogram was shown to be independent predictors of no-reflow phenomenon in patients with acute myocardial infarction (AMI)[7)], and to be associated with a higher incidence of in-hospital and long-term adverse cardiac events in patients with ST-segment elevation myocardial infarction (STEMI)[8–10)]. We also reported that STEMI patients with larger residual thrombus burden after thrombectomy before stent implan-

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tation had more severe microvascular dysfunction, and greater myocardial damage compared with those with smaller residual thrombus[6]. However, the relationship between thrombus after stent implantation and clinical outcomes has not been determined yet.

In the present study, we investigated the incidence of final residual thrombus detected by OCT after stent implantation, and evaluated its clinical impact in STEMI patients.

Methods

Study population and design

The study was a retrospective observational study for STEMI patients consecutively admitted to the Hirosaki University Hospital (Hirosaki, Japan), from January 2014 to July 2017, within 12 hours from the onset of chest pain. STEMI was defined as: 1) continuous typical chest pain of longer than 20 minutes, 2) electrocardiogram showing new ST-segment elevation ≥ 0.2 mV in at least two contiguous precordial leads or ≥ 0.1 mV in at least two adjacent limb leads, new or presumably new left bundle branch block, or a posterior infarction with anterior ST-segment depression on the 12-lead ECG, and 3) elevation above the upper reference limit of troponin T or creatine phosphokinase (CPK)-MB. Exclusion criteria included absence of coronary stenting, absence of post-procedure OCT imaging, and poor image quality. The study was approved by the Ethics Committee of our institution.

OCT imaging acquisition and analysis

We used a frequency-domain OCT system (ILUMIEN OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota) in all cases. Aspirin 200 mg, clopidogrel 300 mg, and heparin 100 IU/kg were administered before the procedure. No patient was pretreated with a thrombolytic agent or a glycoprotein IIb/IIIa inhibitor. Primary PCI was performed using a 6-F or 7-F guiding catheter. Manual aspiration thrombectomy using Rebirth (Goodman Co. Ltd., Nagoya, Japan), Eliminate 3 (Terumo, Tokyo, Japan), Eliminate + (Terumo, Tokyo, Japan), or Export Advance (Medtronic, Minnesota, USA) was performed and repeated to restore antegrade coronary flow. The use of thrombectomy and the number of passes with the aspiration catheter were at the operator's discretion. The technique for using the OCT system was previously described[11]. We evaluated thrombus on OCT images after stenting. A thrombus is identified as an intra-luminal mass, with no direct continuity with the surface of the vessel wall or as a highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal-free shadowing[12], and we defined thrombus as a mass with a diameter ≥ 250 μm attached to the luminal surface, stent strut, or floating within the lumen (Figure 1). For qualitative analysis, all cross-sectional images within the entire length of the stent, plus 5 mm proximal and 5 mm distal reference segments, were analyzed. When the image was poor quality and could not be analyzed, the case was excluded as a poor image quality. Additional thrombectomy was not performed after OCT imaging.

Angiographic analysis

Coronary angiograms were analyzed before PCI, as well as at the end of the procedure. We evaluated final antegrade coronary flow according to the Thrombolysis in Myocardial Infarction (TIMI) criteria[13], and final myocardial blush grades. No-reflow was defined as TIMI flow grade ≤ 2 and/or blush grade ≤ 1 at the final angiogram[14]. Coronary angiograms were analyzed via an offline quantitative coronary angiography (QCA) software (version 5.10.1; Pie Medical Imaging BV, Maastricht, the Netherlands). The reference diameter, minimal lumen diameter, and % diameter stenosis (%DS) at baseline and post procedure were measured.

Echocardiogram analysis

Patients with STEMI had a cardiac ultrasound

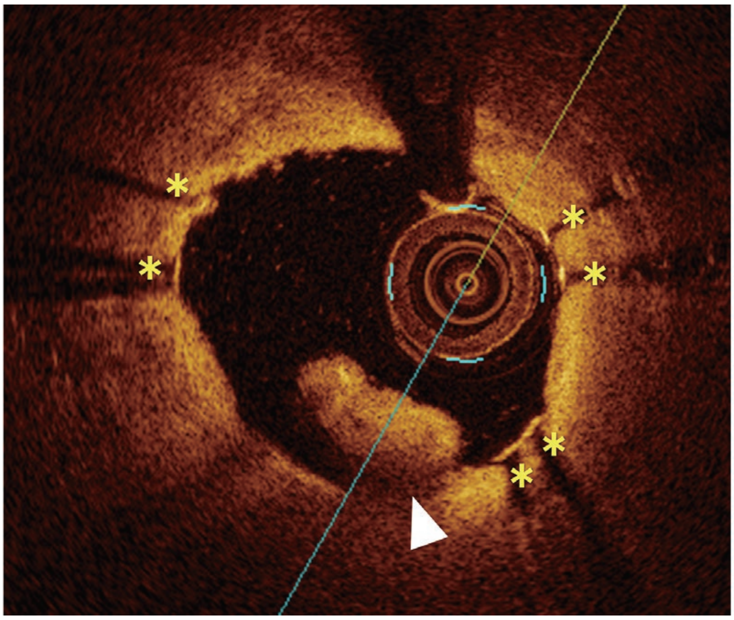

Figure 1. Representative OCT image of thrombus after stenting. Stent struts and thrombus are shown as yellow asterisks and white arrow, respectively.

examination within two weeks after PCI and left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson's rule method.

Statistical analysis

Categorical outcomes were presented as counts and percentages. The mean ± standard deviation was reported when data were normally distributed, and the median (25^{th}–75^{th} percentiles) were reported when data were not normally distributed. We used the Chi-square test or Fisher's exact test for categorical variables. Continuous variables were compared using Student's *t* test or a Wilcoxon rank-sum test on the basis of the distribution. Multivariate logistic regression analysis was performed to assess the relationship between baseline clinical and angiographic characteristics as well as pre-procedural OCT findings, and thrombus. The associated variables in univariate analyses and other potential confounders were included in the multivariate analysis. Further, a stepwise multivariate analysis (forward and backward selection with p=0.25) was done to determine factors independently associated with peak CPK levels, which indicated the myocardial damage. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed with JMP Pro 14.0.0 software (SAS Inc., Cary, NC, USA).

Results

Study population

In the present study, 399 patients with STEMI underwent primary PCI within 12 hours after symptom onset. Patients treated without stenting (n = 59), those without OCT image after stenting procedure (n = 113), those with poor image quality of OCT (n = 15), and those without thrombectomy (n = 32), were excluded from the study (Figure 2). Finally, 180 patients were divided into two groups according to OCT findings after stent implantation: thrombus group (n = 73) and non-thrombus group (n = 107).

Patient's characteristics

Table 1 shows a comparison of basic characteristics between the two groups. Body mass

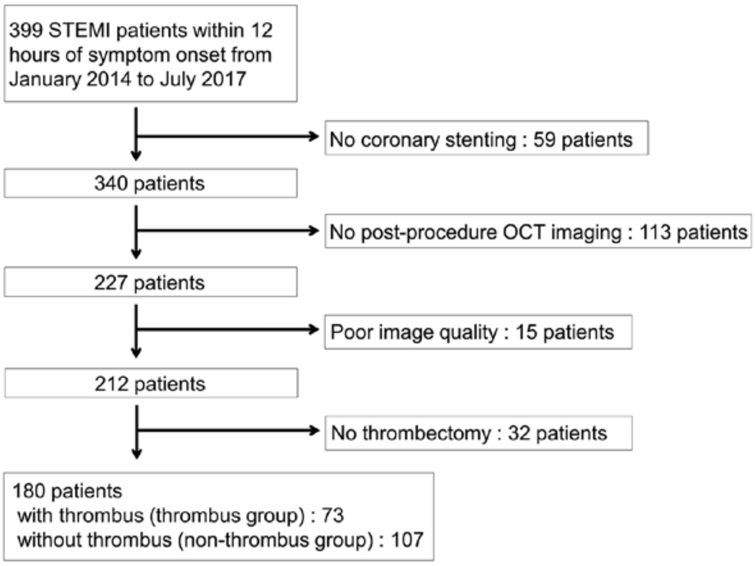

Figure 2. Study flow chart of the present study.

Table 1. Baseline clinical characteristics

	Thrombus group (n=73)	Non-thrombus group (n=107)	p-value
Age (years)	63.8 ± 13.7	66.7 ± 11.6	0.12
Male, n (%)	61 (83.6)	77 (72.0)	0.07
BMI (kg/m^2)	25.1 ± 3.6	24.0 ± 3.0	0.03
Diabetes mellitus, n (%)	22 (30.1)	45 (42.1)	0.10
Hypertension, n (%)	49 (67.1)	71 (66.4)	0.91
Dyslipidemia, n (%)	49 (67.1)	64 (59.8)	0.32
Current smoker, n (%)	37 (50.7)	43 (40.2)	0.16
Previous MI, n (%)	2 (2.7)	5 (4.7)	0.70
Previous PCI, n (%)	3 (4.1)	5 (4.7)	1.00
Laboratory data			
HbA1c, %	5.8 (5.6-6.3)	6.0 (5.6-6.5)	0.21
Blood sugar level, mg/dl	156 (127-205)	162 (133-201)	0.67
HDL-C, mg/dl	43.7 (35.4-51.4)	44.8 (38.0-50.7)	0.54
LDL-C, mg/dl	130 (101-147)	125 (100-148)	0.62
Triglyceride, mg/dl	100 (71-169)	122 (77-158)	0.45
eGFR, mL/min/1.73 m^2	73.4 ± 21.6	70.8 ± 22.8	0.44
hs-CRP, μg/dl	123 (66-248)	94 (32-209)	0.21
Medication on admission			
Statin, n (%)	11 (15.1)	17 (15.9)	0.88
Aspirin, n (%)	8 (11.0)	8 (7.5)	0.42

Values are shown as mean ± standard deviation, median (25^{th}-75^{th} percentiles), or n (%). BMI indicates body mass index, MI; myocardial infarction, PCI; percutaneous coronary intervention, HbA1c; hemoglobin A1c, HDL-C; high-density lipoprotein cholesterol, LDL-C; low-density lipoprotein cholesterol, eGFR; estimated glomerular filtration rate, hs-CRP; high sensitive C-reactive protein, CPK; creatine phosphokinase, CPK-MB; creatine phosphokinase-MB.

index (BMI, kg/m^2) was significantly greater in the thrombus group than in the non-thrombus group (25.1 ± 3.6 vs. 24.0 ± 3.0, $p = 0.03$). There were no differences in the other variables between the two groups.

PCI and OCT findings

Table 2 summarizes the angiographic characteristics and PCI procedural findings. There

Table 2. Angiographic characteristics and procedural parameters

	Thrombus group (n=73)	Non-thrombus group (n=107)	p-value
Culprit vessels			
RCA, n (%)	38 (52.1)	60 (56.1)	0.36
LAD, n (%)	6 (8.2)	14 (13.1)	
LCx, n (%)	28 (38.4)	33 (30.8)	
LMT, n (%)	1 (1.4)	0 (0)	
Multivessel disease, n (%)	22 (30.6)	42 (39.3)	0.23
QCA analysis			
Baseline			
Reference diameter, mm	2.49 ± 0.79	2.37 ± 0.64	0.23
MLD, mm	0.28 ± 0.41	0.32 ± 0.41	0.46
% diameter stenosis, %	87.1 ± 19.0	86.6 ± 16.6	0.84
Post-procedure			
Reference diameter, mm	3.05 ± 0.54	2.92 ± 0.50	0.08
MLD, mm	2.66 ± 0.51	2.57 ± 0.45	0.18
% diameter stenosis, %	12.6 ± 7.3	12.5 ± 8.6	0.97
PCI procedure			
DES, n (%)	27 (37.0)	36 (33.6)	0.64
Number of stent >1, n (%)	4 (5.5)	10 (9.4)	0.34
Stent size, mm	3.2 ± 0.48	3.1 ± 0.47	0.05
Total stent length, mm	22.7 ± 6.4	23.6 ± 9.8	0.49
Time from onset to balloon, min	220 (166-320)	241 (173-366)	0.22

Values are shown as mean ± standard deviation, median (25^{th}-75^{th} percentiles), or n (%). RCA indicates right coronary artery, LAD; left anterior descending artery, LCx; left circumflex artery, LMT; left main coronary trunk, QCA; quantitative coronary angiography, MLD; minimal lumen diameter, DES; drug-eluting stent.

Table 3. Optical coherence tomography findings

	Thrombus group (n=73)	Non-thrombus group (n=107)	p-value
Minimal stent area, mm^2	6.9 ± 2.2	6.1 ± 2.0	0.01
Minimal lumen area, mm^2	6.2 ± 1.9	5.6 ± 1.8	0.03

Values are shown as mean ± standard deviation.

were no significant differences in culprit vessels, QCA analyses, and PCI procedural parameters between the two groups. Furthermore, no difference was found in stent type (bare metal stent or drug-eluting stent) between the two groups. Minimal stent area (MSA, mm^2) on OCT images after stenting were significantly larger (6.9 ± 2.2 vs. 6.1 ± 2.0, p = 0.01) and minimal lumen area (MLA, mm^2) was also greater (6.2 ± 1.9 vs. 5.6 ± 1.8, p = 0.03) in the thrombus group than in the non-thrombus group (Table 3). However, adjusted multivariate analysis showed that none of them were independently associated with thrombus after stenting (Table 4).

<u>Clinical significance</u>

No-reflow and peak CPK, which indicate microvascular dysfunction and myocardial damage respectively, were compared as clinical outcomes between the two groups. There were no significant differences in the number of patients with no-reflow between the two groups (Table 5). Peak CPK levels were greater in the thrombus group than in the non-thrombus group with close to significance (3649 {1752-7053} vs. 2563 {1201-4282} IU/L, p = 0.053). Furthermore, LVEF did not differ between the two groups.

Table 4. Multivariate analysis for thrombus after stenting

	OR	95% CI	p-value
Age	1.00	0.97-1.03	0.86
Male	1.73	0.76-4.14	0.20
Minimal lumen area, mm^2	0.25	0.73-1.04	0.13
BMI	0.19	0.83-1.02	0.11

OR indicates odds ratio. CI; confidence interval, BMI; body mass index. All parameters above were included in multivariate analysis.

Table 5. Comparison of clinical outcomes between the two groups

	Thrombus group (n=73)	Non-thrombus group (n=107)	p-value
Peak CPK, IU/L	3649 (1752-7053)	2563 (1201-4282)	0.05
Peak CPK-MB, IU/L	337 (223-619)	283 (123-467)	0.09
No reflow, n (%)	15 (21.4)	24 (23.5)	0.75
LVEF (modified Simpson), %	51.6 ± 11.0 (n=68)	53.2 ± 12.6 (n=107)	0.39

Values are shown as mean ± standard deviation, median (25^{th}-75^{th} percentiles), or n (%). CPK indicates creatine phosphokinase, CPK-MB; creatine phosphokinase-MB. LVEF; left ventricular ejection fraction.

Table 6. A stepwise multivariate analysis for peak CPK levels

	Coefficient (β)	SEM	p-value
Male, n (%)	0.171	277.3	0.02
BMI (kg/m^2)	0.092	88.6	0.22
Dyslipidemia, n (%)	−0.104	243.4	0.16
Previous PCI, n (%)	−0.125	562.8	0.08
Thrombus, n (%)	0.148	240.4	0.046

SEM indicates standard error of the mean.

To further investigate relationship between peak CPK levels and thrombus after stenting, a stepwise multivariate analysis was performed. We included patients' characteristics relating with risk factors (age, sex, BMI, diabetes mellitus, hypertension, dyslipidemia, current smoker, previous PCI), OCT analysis (minimal lumen area), and thrombus to the stepwise analysis. Selected parameters after stepwise forward/backward selection were sex, BMI, dyslipidemia, previous PCI, and thrombus. The analysis finally revealed that male (p=0.02) and residual thrombus after stenting (p=0.046) were significantly associated with peak CPK levels (Table 6).

Discussion

Major findings

The main findings of the present study include: 1) thrombus after stent implantation was detected by OCT in 41% of STEMI patients, 2) patients with residual thrombus had significantly larger MSA and MLA in post-procedure OCT images in unadjusted analysis, but not in multivariate analysis, 3) patients with residual thrombus on OCT after stent implantation had greater myocardial damage evaluated by peak CPK levels compared with those without thrombus, and 4) the presence of residual thrombus after stent implantation was independently associated with the peak CPK levels. All these findings indicate clinical significance of thrombus evaluated by OCT after stent implantation in STEMI patients.

Detection of thrombus by OCT in STEMI patients

Hong et al. reported that IVUS-detected tissue prolapse, an intraluminal tissue (plaque and/or thrombus) extrusion through the stent struts, was present in 34% of AMI patients after stent implantation. They further showed that it was associated with poor short-term outcomes (acute and subacute thrombosis and no-reflow phenomenon), but not associated with long-term outcomes at 1 year after stent implantation[15]. Furthermore, Prati et al. reported that OCT-detected intrastent plaque/thrombus protrusion >500 μm during PCI was present in 29% of angina patients (56% ACS and 44% SAP). They further showed that suboptimal stent deployment was associated with an increased risk of major adverse cardiac events, but intrastent plaque/thrombus protrusion was not associated with worse outcome[16].

In the present study, we evaluated AMI patients within 12 hours from the onset who had much thrombus and required thrombectomy. Consistent with the previous studies, OCT-detected thrombus after stent implantation was detected in 41% of the patients. This finding indicates that the most of thrombus on angiogram was effectively eliminated by anti-platelet drugs, heparin administration, thrombectomy, and stenting, but still relatively small thrombus detected by OCT was present after stent implantation in some patients. Multivariate analysis demonstrated none of independent predictors for thrombus after stent implantation, suggesting that unknown factors may be associated with residual thrombus. Further studies are clearly needed to unravel underlying mechanism for residual thrombus after stent implantation.

Clinical significance of thrombus in STEMI patients

We previously showed that OCT-detected residual thrombus after thrombectomy before stent implantation was present in STEMI patients, and a greater residual thrombus was associated with worse microvascular dysfunction and greater myocardial damage[6]. In the present study, we investigated clinical significance of residual thrombus after stent implantation. We found that peak CPK levels were higher in patients with thrombus after stent implantation with close to significance and thrombus was an independent predictor for peak CPK levels. These findings strongly indicate that OCT-detected residual thrombus before and after stent implantation is one of the important predictors for myocardial damage in STEMI patients and may be a therapeutic target to reduce myocardial damage.

Study limitations

This study has several limitations. First, this was a retrospective observational study. Although all STEMI patients undergoing PCI with coronary stenting were eligible for inclusion in this study, OCT was performed at the operator's discretion and therefore the study population may have had potential selection bias. In addition, the aspiration thrombectomy before stenting was also performed at the operator's discretion, which may have affected the results. Second, although we evaluated peak CPK and CPK-MB levels as a marker for myocardial damage, other assessments using the modality such as cardiac single photon emission computed tomography may also be useful for evaluation of myocardial damage. Third, additional large-scale studies are required to confirm the presented data, because this study was conducted using a relatively small sample size at a single center. Moreover, impact of residual thrombus on long-term prognosis is also of interest. Finally, further definition of standardized OCT optimization criteria and also optimal surrogate and clinical endpoints will be required to improve acute results of coronary interventions. Although there are several limitations, the present study may provide an important clinical implication to improve prognosis of STEMI patients.

Conclusions

Residual thrombus after stent implantation evaluated by OCT was detected in 41% STEMI patients. Importantly, residual thrombus was an independent predictor for peak CPK levels, indicating that OCT-detected thrombus may be associated with myocardial damage in STEMI patients. Further studies to investigate underlying mechanism are warranted.

Conflicts of interest

Dr. Yokota is an associate professor and Dr. Tomita is a concurrent professor in the endowed department (the Advanced Cardiovascular Therapeutics) by Abbott Vascular Japan. For the remaining authors, there are no conflicts of interest.

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