Original article

Longitudinal extent of lipid pool assessed by optical coherence tomography predicts microvascular no-reflow after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

\textit{Background:} Distal embolization during percutaneous coronary intervention (PCI) may deteriorate microvascular reperfusion in patients with ST-elevation myocardial infarction (STEMI). Reperfusion at the coronary microvascular level is important for STEMI and culprit plaque is associated with distal embolization and microvascular reperfusion. ST-segment resolution (ST-R) in the electrocardiogram reflects microvascular reperfusion after primary PCI. Longitudinal extent of lipid pool assessed by optical coherence tomography (OCT) may predict the risk of failure of microvascular reperfusion after primary PCI.

\textit{Methods and results:} This study consisted of 39 patients with STEMI who underwent primary PCI within 24 h after the onset of chest pain. Immediately after thrombectomy, OCT was performed and length of lipid pool was measured. Microvascular reperfusion after primary PCI was assessed by ST-R, which was defined as >50% decrease in ST elevation at 1 h after primary PCI.

There were 23 patients with ST-R and 16 patients without ST-R, with no significant difference in baseline clinical and angiographical variables between the 2 groups. Final thrombolysis in myocardial infarction 3 flow was obtained in all of the patients. Peak creatine kinase was significantly higher in the ST-R (−) group than in the ST-R (+) group \((p = 0.01)\). Length of lipid pool was 10.1 ± 2.8 mm in the ST-R (−) group and 7.8 ± 3.2 mm in the ST-R (+) group \((p = 0.02)\). In receiver operating characteristics curve assessing the ability of length of lipid pool to predict ST-R, area under the curve was 0.74 \((p = 0.02)\). Length of lipid pool >9.0 mm best predicted the absence of ST-R with sensitivity 88% and specificity 78%.

\textit{Conclusions:} These findings suggest that length of lipid pool estimated by OCT may predict microvascular no-reflow after primary PCI.

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\textbf{Introduction}

Primary percutaneous coronary intervention (PCI) is a well-established reperfusion strategy for ST-segment elevation myocardial infarction (STEMI) patients [1]. However, distal embolization during PCI may deteriorate microvascular reperfusion for STEMI patients and may cause no-reflow phenomenon [2–5]. Despite early restoration of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct related artery (IRA), microvascular reperfusion may fail to be acquired in a substantial portion of the jeopardized myocardium [2–7] and no-reflow phenomenon is associated with worse long-term outcome after STEMI [8]. ST-segment resolution (ST-R) on the electrocardiogram (ECG) reflects myocardial flow and microvascular reperfusion after primary PCI rather than epicardial flow and predicts better myocardial salvage and clinical outcome [9,10]. Numerous efforts have been made to detect high-risk plaque which may cause no-reflow after primary PCI, using several imaging devices. Of these, intravascular ultrasound...
(IVUS) was most frequently used for this purpose. Several reports have suggested that culprit lesion assessment by IVUS could predict distal embolization and a large infarct size during PCI and large lipid-rich plaque at culprit lesions may be associated with no-reflow phenomenon [11–13]. Although IVUS can assess plaque volume and, using several signal processing methods, may obtain tissue character information, resolution of IVUS is relatively low. Optical coherence tomography (OCT) has been recently developed as a high-resolution imaging method to observe culprit lesions more clearly. It also provides clear images of lipid pool which may have great risk of no-reflow if PCI is performed. There are few data on the prognostic utility of OCT in patients with STEMI who underwent primary PCI. This study was undertaken to assess the association between longitudinal extent of lipid pool assessed by OCT and microvascular reperfusion estimated by ST-R.

Methods

Study patients

We enrolled 39 patients with STEMI who underwent primary PCI and performed OCT within 24 h after symptom onset from May 2008 to February 2010 at Hiroshima City Hospital. We excluded patients with culprit lesions in the left main trunk, ostium lesions, extremely tight lesions or tortuous vessels where we expected difficulty in advancing the OCT catheter, and target vessel reference diameter of ≥4 mm expected limitation in OCT evaluation. All patients were treated by aspiration thrombectomy and stent deployment without any distal protection device. Further, we excluded patients with angiographic no-reflow to focus on the microvascular no-reflow phenomenon. STEMI was diagnosed by chest pain consistent with ongoing myocardial ischemia persisting longer than 30 min with ST-segment elevation of >0.1 mV in 2 limb leads or >0.2 mV in 2 contiguous precordial leads, and a rise in serum creatine kinase (CK) levels to more than twice the upper limit of normal. CK was measured every 3 h. Emergency coronary angiography and primary PCI were performed in a manner as previously reported [14]. Selective coronary angiography was performed in multiple projections before the initiation of reperfusion therapy. Immediately after diagnostic angiography, primary PCI was performed. OCT was performed after getting TIMI flow grade 3 by aspiration thrombectomy. Informed consent was obtained from each patient. This study was approved by the ethical committee at Hiroshima City Hospital.

OCT procedures

The OCT system was the LightLab M2 TD-OCT Imaging System (LightLab, Westford, MA, USA). A 0.016-in. OCT catheter was advanced to the distal end of the culprit lesion, and to remove the blood from the view, the 3-Fr occlusion balloon was inflated to 0.5 atm at proximal site of the lesion and lactate Ringer’s solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 ml/s. The entire length of the culprit lesion was imaged with an automatic pullback device moving at 1 mm/s, and the OCT image clearly visualized the culprit lesion [15,16].

OCT image analysis

All images were stored digitally for subsequent analysis. Analysis of the OCT images was performed by 2 reviewers blinded to the results of the ECG analyses. OCT images were analyzed using validated criteria for thrombus characterization, plaque characterization, and fibrous cap thickness was determined as reported previously [15–23]. Red thrombi were defined as high-backscattering protrusions inside the lumen of artery, with signal-free shadow, white thrombi were defined as signal-rich, low-backscattering protrusions, and mixed thrombi were defined as mixture with both characteristics. Thrombus was semiquantified as the number of involved quadrants on the cross-sectional OCT image. Lipid pool was characterized by a signal-poor region in OCT image (Fig. 1A, white arrows). Lipid was semiquantified as the number of involved quadrants on the cross-sectional OCT image. Lipid-rich plaque was defined as plaque with ≥2 quadrants. Briefly, fibrous cap thickness was defined as the minimum distance from the coronary artery lumen to inner border of lipid pool (Fig. 1B, red arrow). Cap thickness for each image was measured 3 different times, and the average value was computed. When lipid was present in ≥2 quadrants in any of the images within a plaque, it was considered a lipid-rich plaque. For each patient, the cross-sectional image with the thinnest fibrous cap was used for analysis. The thin cap fibroatheroma (TCFA) was defined as a plaque with lipid content in ≥2 quadrants and the thinnest part of the fibrous cap measuring <65 μm. Culprit plaque was defined as the ruptured plaque or the plaque with the thinnest fibrous cap or thrombus. The length of lipid pool was measured as consecutive longitudinal length of lipid pool at culprit plaque assessed by OCT (Fig. 2). Cross-sectional views correspond to the sections indicated by A, B, C, and D on the longitudinal views. Thrombus was observed in

Fig. 1. Lipid pool and fibrous cap thickness in optical coherence tomography (OCT). Lipid pool was characterized by a signal-poor region in OCT image (A, white arrows). The square of broken white lines in A was expanded to B. Fibrous cap thickness was defined as the minimum distance from the coronary artery lumen to inner border of lipid pool (B, red arrow). (For interpretation of references to color, in this figure legend, the reader is referred to the web version of this article.)
B and plaque rupture was observed in C. This plaque was defined as culprit plaque. If detection of consecutive lipid pool was difficult due to a lot of red thrombus, consecutiveness of culprit plaque was evaluated using many distal or proximal sagittal frames and landmarks such as side branches.

**ECG analysis**

A 12-lead ECG was recorded on admission and 1 h after the final angiogram, at a paper speed of 25 mm/s and an amplification of 10 mm/mV. ST-R was defined as >50% decrease of ST segment elevation at 1 h after primary PCI at the lead in which ST segment elevation was greatest on the initial electrocardiogram [9,24]. Patients were stratified into two groups based on ST-R; ST-R (+) group (n = 23) was compared with ST-R (−) group (n = 16).

**Statistical analysis**

We used standard statistical methods. We tested the significance of difference with χ² test for categorical variables. Student’s t test was used for continuous variables. We used the JMP statistical package (version 5.0.1); SAS, Cary, NC, USA) for all statistical tests. A significance level of 0.05 was used and two-tailed tests were applied.

**Results**

ST-R (−) was observed in 16 of 39 patients (41.0%). Clinical characteristics of the study patients are shown in Table 1. There was no significant difference in these clinical variables between the ST-R (+) and ST-R (−) groups. There was a tendency toward longer time from onset to angiography in the ST-R (−) group, but the difference did not reach statistical significance. No significant differences in implanted stent length, implanted stent diameter, and balloon inflation pressure were observed between the ST-R (+) and ST-R (−) groups (implanted stent length: 18.8 ± 5.6 mm vs. 19.7 ± 5.6 mm, p = 0.61; implanted stent diameter: 3.22 ± 0.36 mm vs. 3.10 ± 0.35 mm, p = 0.32; inflation pressure: 13.5 ± 2.2 atm vs. 13.8 ± 2.6 atm, p = 0.68). Angiographical characteristics of the study patients are shown in Table 2. There was no significant difference in infarct location, initial TIMI flow grade 0–1, multivessel disease, collateral flow, reference vessel diameter, and minimal lumen diameter between the ST-R (+) group and the ST-R (−) group. All patients achieved final TIMI 3 flow grade. Although 6 patients had TIMI 2 flow grade after stent deployment, they achieved final TIMI

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics.</th>
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<tr>
<td></td>
<td>ST-R (+)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63 ± 12</td>
</tr>
<tr>
<td>Male</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (43%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (47%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13 (56%)</td>
</tr>
<tr>
<td>Time to angiography (h)</td>
<td>3.3 ± 3.9</td>
</tr>
<tr>
<td>Killip class 3–4</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Medications on admission</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>βblocker</td>
<td>0 (0%)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Angiographical characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ST-R (+)</td>
</tr>
<tr>
<td>Culprit vessel</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>8 (34%)</td>
</tr>
<tr>
<td>LCX</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>RCA</td>
<td>14 (60%)</td>
</tr>
<tr>
<td>Initial TIMI flow grade 0–1</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>Final TIMI flow grade 3</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>10 (43%)</td>
</tr>
<tr>
<td>Collateral flow</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>3.25 ± 0.37</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>0.62 ± 0.22</td>
</tr>
</tbody>
</table>

3 flow grade after intracoronary administration of nirocanidil. Peak CK was significantly higher in the ST-R (−) group than in the ST-R (+) group (4249 ± 2377 IU/l vs. 2479 ± 1750 IU/l, p = 0.01, Fig. 3). OCT findings of the study patients are shown in Table 3. Thrombi were observed in all patients. After aspiration thrombectomy, residual thrombus tended to be more frequently found by OCT in the ST-R (−) group than the ST-R (+) group (p = 0.07). Residual red thrombus was found in 9 patients in the ST-R (+) group and in 5 patients in the ST-R (−) group (p = 0.61). Residual white thrombus was found in 12 patients in the ST-R (+) group and in 10 patients in the ST-R
Fig. 3. Peak creatine kinase (CK) in patients without ST-segment resolution (ST-R) (−) and those with ST-R (+). Peak CK was significantly higher in the ST-R (−) group than in the ST-R (+) group (4249 ± 2377 IU/l vs. 2479 ± 1750 IU/l).

Table 3

<table>
<thead>
<tr>
<th>Culprit plaque</th>
<th>ST-R (+) (n=23)</th>
<th>ST-R (−) (n=16)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red/white/mixed</td>
<td>9/12/2</td>
<td>5/10/1</td>
<td>0.61/0.52/0.77</td>
</tr>
<tr>
<td>No. of quadrants, 1/2/3/4</td>
<td>5/8/7/3</td>
<td>0/5/6/5</td>
<td>0.07</td>
</tr>
<tr>
<td>Plaque rupture</td>
<td>15 (65%)</td>
<td>8 (50%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Fibrous cap thickness, μm</td>
<td>79±74</td>
<td>54±30</td>
<td>0.20</td>
</tr>
<tr>
<td>Lipid plaque, no. of quadrants</td>
<td>2/1/1/2</td>
<td>1/1/1/1/2</td>
<td>0.97</td>
</tr>
<tr>
<td>Lipid-rich plaque</td>
<td>21 (91%)</td>
<td>15 (93%)</td>
<td>0.75</td>
</tr>
<tr>
<td>TCFA</td>
<td>14 (60%)</td>
<td>12 (75%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Length of lipid pool, mm</td>
<td>7.8±3.2</td>
<td>10.1±2.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ST-R, ST-segment resolution; TCFA, thin cap fibroatheroma.

(p = 0.52). There was no significant difference in thrombus characterization, plaque rupture, fibrous cap thickness, and the incidence of TCFA between the ST-R (+) and ST-R (−) groups. However, length of lipid pool was significantly higher in the ST-R (−) group than in the ST-R (+) group (Fig. 4). Receiver operating characteristics (ROC) curve assessing ability of length of lipid pool to predict ST-R after primary PCI is shown in Fig. 5. The area under the curve was 0.74 (p = 0.02). Length of lipid pool >9.0 mm best predicted the absence of ST-R, with a sensitivity of 88% and specificity of 78%. Peak CK was significantly higher in patients with length of lipid pool >9.0 mm than those without (3968 ± 2504 IU/l vs. 2481 ± 1578 IU/l, p = 0.03).

Fig. 4. Relation between length of lipid pool estimated by optical coherence tomography (OCT) and ST-segment resolution (ST-R). Length of lipid pool was significantly higher in the ST-R (−) group than in the ST-R (+) group.

Fig. 5. Receiver operating characteristics to determine the optimal cut-off value for the length of lipid pool to predict ST-segment resolution (ST-R) (−). The area under the curve was 0.74 (p = 0.02). Length of lipid pool >9.0 mm best predicted the absence of ST-R, with a sensitivity of 88% and specificity of 78%.

Discussion

The major finding of the present OCT study was that length of lipid pool estimated by OCT may predict ST-R after primary PCI. In addition, there was no significant difference between number of lipid plaques, fibrous cap thickness, and TCFA assessed by cross-sectional OCT images and ST-R.

Previous studies have shown that abnormalities at the level of the microvasculature cause no-reflow phenomenon during reperfusion after prolonged coronary artery occlusion [25,26]. The pathogenetic cause of no-reflow phenomenon is multifactorial. The capillary structure becomes disorganized in the no-reflow zone because of endothelial dysfunction, compression by tissue, myocyte edema, neutrophil infiltration, the generation of oxygen free radicals, and distal embolism [27–29]. In humans, no-reflow is caused by the variable combination of 4 pathogenetic components: (1) distal atherothrombotic embolization; (2) ischemic injury; (3) reperfusion injury; and (4) susceptibility of coronary microcirculation to injury [30]. In addition to ischemic injury and reperfusion injury in patients with STEMI undergoing primary PCI, distal embolization of disrupted plaque contents and residual thrombus may lead to progressive decline of coronary flow and further deteriorate no-reflow [31]. Thus, it has clinical importance to estimate the lesion probability of distal embolization for the prediction of no-reflow phenomenon.

Several methods, including coronary angiography (myocardial blush grade), myocardial contrast echocardiography, and magnetic resonance imaging have been used to assess microvascular reperfusion. Electrocardiographic assessment of ST-R is one of the established measures for microvascular reperfusion. Numerous studies have shown a remarkably consistent relationship between ST-R and subsequent mortality [10,32,33]. Notably, it was reported that approximately one-third of patients with TIMI flow grade 3 and myocardial blush grade (MBG) 2–3 do not exhibit ST-R [34]. In the current study, where final TIMI 3 flow grade was achieved in all study patients, ST-R (−) was observed in 41% patients and peak CK was significantly higher in ST-R (−) than in ST-R (+). Although all patients achieved final TIMI 3 flow grade in our study, angiographic no-reflow was reported to occur in 5–6% of STEMI patients.
Funding

patients with large vessel diameter may have led to all patients achieving final TIMI3 flow grade.

Previous studies have reported that a high atherothrombotic burden and a decrease in plaque volume as assessed by IVUS during PCI were associated with microvascular reperfusion after PCI in patients with STEMI [37]. In the current study, we evaluated number of lipid pool, fibrous cap thickness, and TCFA as a cross-sectional OCT image at culprit lesions. However, we could not find any significant correlations between cross-sectional OCT images and ST-R. These findings suggested that it may be insufficient to evaluate only one cross-sectional OCT image to quantify accurate plaque burden. To evaluate longitudinal extent of lipid at multi cross-sectional OCT images may be needed to quantify the whole plaque burden accurately. With high image resolution, OCT can evaluate lipid pool clearly, because OCT could identify edge of lipid to minimize the effect of artifacts such as thrombus and calcification.

To prevent no-reflow phenomenon during PCI, several trials have been conducted with a variety of embolic distal protection devices. However, conflicting results have cast doubt on whether the routine use of embolic protection devices is warranted [30,38]. The Drug Elution and Distal Protection in ST Elevation Myocardial Infarction (DEDICATION) trial suggested that in primary PCI for STEMI, the routine use of distal protection increased the incidence of stent thrombosis and clinically driven target lesion/vessel revascularization [39]. Therefore, it is necessary to determine patients who will suffer from embolic obstruction and no-reflow after PCI without distal protection devices. Prospective studies will be advocated to investigate the propriety of OCT-guided use of distal protection devices to prevent no-reflow during primary PCI for AMI.

Study limitations

The major limitation of this study is small sample size. Because of the invasive nature of this study, only 39 patients were included. Microvascular no-reflow was assessed by electrocardiographic ST-R. Use of other measures, including MBG by coronary angiography, microvascular obstruction by magnetic resonance imaging, and contrast deficit by contrast echocardiography, might have provided additional information on microvascular reperfusion. OCT was used as the only intravascular imaging modality. Comparison of findings of OCT to those of IVUS or angiography was not performed.

Aspiration thrombectomy was performed routinely before the OCT examination. This procedure may affect the plaque and thrombus morphology. This study has patient selection bias. The patients with angiographic no-reflow were excluded. Because of the nature of OCT, this study had no other choice than to exclude patients with large vessel, severe stenosis, and tortuous coronary lesions. Inability to measure plaque volume is one of the major limitations of OCT. This may have affected the results.

Conclusions

The presence of longer culprit lipid pool as estimated by OCT was associated with a higher incidence of ST-R (−). These findings suggest that longitudinal evaluation of lipid pool by OCT may predict microvascular no-reflow after primary PCI. Further studies should be advocated to investigate the better therapeutic options for high-risk patients to reduce microvascular no-reflow.

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Disclosures

None.

References


