Development of lipid-rich plaque inside bare metal stent: possible mechanism of late stent thrombosis? An optical coherence tomography study

Jingbo Hou,1 Hai Qi,1 Maomao Zhang,1 Lijia Ma,1 Huimin Liu,1 Zhigang Han,1 Lingbo Meng,1 Shuang Yang,1 Shaosong Zhang,2 Bo Yu,1 Ik-Kyung Jang3

ABSTRACT

Aims To study in-stent tissue characteristics by optical coherence tomography (OCT) at long-term follow-up in patients with previous bare metal stent implantation.

Methods and results Among 1636 patients who underwent bare metal stent (BMS) implantation between 1999 and 2006, 39 patients with 60 BMS who developed recurrent ischaemia underwent repeat catheterisation and OCT imaging between June 2008 and August 2009. The average time interval between initial BMS implantation and OCT imaging was 6.5±1.3 years. A lesion that had features of lipid-rich plaque was found in 20 stents (33.3%) in 16 patients (41%). Fibrous intima was observed in the remaining 40 stents. In the group with lipid-rich plaque, average fibrous cap thickness was 56.7±5.8 μm and lipid arc was 173±58. Six patients had evidence of recent plaque disruption and another six patients had mural thrombus. Hypertension and smoking were more common in these patients than in those with fibrous intima.

Conclusions Lipid-rich plaque with a thin fibrous cap was seen in patients with previous BMS implantation and recurrent ischaemia at late follow-up. This may be one possible mechanism for late stent thrombosis.

Very late stent thrombosis (VLST) is associated with a high incidence of acute myocardial infarction and mortality.1–4 Although more common after drug-eluting stent implantation, VLST also occurs after bare metal stent (BMS) implantation.5 6 The mechanism of this late catastrophic complication is not fully understood. It is generally thought that lack of stent struts surface coverage and late malapposition may be responsible for VLST after drug-eluting stent implantation. However, the exact mechanism, especially for bare metal stents, is largely unknown.

A recently introduced high-resolution optical coherence tomography (OCT) may provide an opportunity to study possible mechanisms of late tissue coverage after stent implantation.

PATIENTS AND METHODS

Patient population

Between 1999 and 2006, 1636 patients underwent a percutaneous coronary intervention procedure with BMS for de novo native coronary lesions. Between June 2008 and August 2009, 92 patients returned with recurrent ischaemia. Among these patients 59 gave consent for intravascular OCT imaging. The average time between the stenting and OCT imaging follow-up was 6.5±1.3 years. The patients’ baseline characteristics are shown in table 1. Patients were excluded if they had significant left main disease, congestive heart failure or renal insufficiency (creatinine>1.8 mg/dl). In addition, those with extremely tortuous vessels or with heavy calcification were excluded because of expected difficulty in advancing the OCT catheter. Demographic and clinical data were collected. This protocol was approved by the Harbin Medical University Ethics Committee, and all patients signed an informed consent before the catheterisation procedure.

Angiographic analysis

Coronary angiograms were analysed using a quantitative coronary angiogram program7 by two angiographers who were blinded to the clinical protocol. In-stent restenosis (ISR) was defined as ≥50% diameter stenosis at follow-up.

OCT image acquisition

The technique of intracoronary OCT imaging has been previously described.3 In brief, a 0.016 inch OCT catheter (Image Wire, LightLab Imaging, Westford, Massachusetts, USA) was advanced to the distal end of the stent through a 3-F occlusion balloon catheter. In order to remove blood from the field of view, an occlusion balloon was inflated to 0.5–0.7 atm at the proximal site of the stent, and lactate Ringer’s solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5–2.0 ml/s by a high-pressure injector. The entire length of the culprit lesion was imaged with an automatic pullback device at 3 mm/s.

OCT data collection and analysis

OCT images were analysed by two independent investigators who were blinded to the clinical presentations. When there was discordance between the observers, a consensus reading was obtained. In-stent plaques were categorised using the previously established criteria.9

Statistical analysis

Data were expressed as mean±SD or median with range. Baseline characteristics were analysed using the χ2 test or Fisher exact test. Unpaired numerical data obtained were compared by the unpaired t test. A Kruskal–Wallis test was performed for data which were not normally distributed. All analysis was performed using SPSS 17.0. A p value <0.05 was required for statistical significance.
RESULTS

Patient characteristics
In 39 patients, a previous BMS was the culprit site in seven (17.9%) patients. The culprit lesion for the remaining 32 patients was not previously treated. The clinical presentations of these patients are shown in table 2. The majority of patients presented with acute coronary syndromes.

Angiographic findings
Thirty three stents were placed in the left anterior descending coronary artery, 12 in the circumflex, and 15 in the right coronary artery. Angiographic ISR occurred in 24 (40.0%) stents. The mean minimal luminal diameter for 24 stents with ISR was 1.1 ± 0.3 mm, while the reference vessel diameter was 2.9 ± 0.5 mm (62.1% diameter stenosis). The mean stent diameter and minimal luminal diameter for all 60 stents were 3.0 ± 0.5 mm and 1.8 ± 0.8 mm, respectively. Only one patient had overlapping stents in the right coronary artery and had restenosis at the overlapping site.

OCT findings
Among 60 stents in 39 patients, 20 stents (33.3%) in 16 patients had lipid-rich plaque (LRP) inside the stents. Thirteen of these 20 stents (65%) met the angiographic definition of ISR. Seven restenotic lesions with LRP were responsible for unstable angina (35%) had macrophage in lipid-rich plaques had evidence of plaque disruption and one ruptured. Because the samples were acquired by directional coronary atherectomy, a thorough study of the atherosclerotic plaque was impossible. Takano et al16 reported that neointima within the BMS often transforms into lipid-laden tissue during an extended period of time, and four patients with acute coronary syndrome had angiographic ISR and OCT findings of lipid-laden intimal disruption and thrombus.

In our study, the tissue inside the stent was characterised using the previously validated OCT criteria. The exact mechanism for the development of LRP inside old BMS is unclear. Since

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 39</th>
<th>Previous BMS</th>
<th>New lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up period (years)</td>
<td>6.5 ± 1.3</td>
<td>7 (17.9)</td>
<td>32 (82.1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.5 ± 9.3</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>30 (76.9)</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>22 (56.4)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diabetics, n (%)</td>
<td>14 (35.9)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>8 (20.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>28 (71.8)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*STEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

Baseline characteristics between patients with and without in-stent lipid-rich plaque
Baseline characteristics did not differ between the patients with and without in-stent LRP. Hypertension and smoking were more common in patients with in-stent LRP (p < 0.05) (table 3).

DISCUSSION

The paradigm of plaque stabilisation by stents (especially BMS) was broadly accepted. However, in spite of the initial efficacy and stability of coronary stenting, a concern was recently raised for the long-term safety of implanted metal stents.10–14

In this paper, we report, for the first time to our knowledge, that new atherosclerotic plaque-like tissue, especially LRP-type, appeared to develop inside the previous BMS in some cases after 6.5 ± 1.3 years of stenting. Among 20 stents with LRP, seven (35%) had macrophage infiltration and six showed evidence of fibrous cap disruption, indicating instability of this type of plaque.

Hasegawa et al15 analysed 14 samples of stenotic tissues inside BMS retrieved by directional coronary atherectomy. In their study, new atherosclerotic progression was seen in all cases in healed neointimal tissue inside a stent at long-term follow-up. Based on these samples, they concluded that the LRP is a future target for successful long-term treatment of coronary restenosis.

In our study, the tissue inside the stent was characterised using the previously validated OCT criteria. The exact mechanism for the development of LRP inside old BMS is unclear. Since
stent struts cover only about 15% of vessel surface, it is conceivable that new atherosclerotic tissue grows from the vessel wall through the space between struts into the lumen.\textsuperscript{17-18} Surprisingly, in 20 stents (35% of stents), the tissue inside the stent appeared to be rich in lipid covered by a thin fibrous cap. Evidence of recent fibrous cap rupture was seen in six of these 20 stents.\textsuperscript{19} All of these six patients presented with unstable angina pectoris. These findings indicate that disruption of the fibrous cap of LRP inside the stent may be one possible mechanism for recurrent ischaemia at late stage.

Although VLST has been reported more frequently with drug-eluting stents,\textsuperscript{1-4} this late catastrophic complication has also been reported following BMS implantation.\textsuperscript{5,6} Histology and OCT studies showed that uncovered stent struts and malapposition were more common in patients with drug-eluting stents.\textsuperscript{20} This LRP-like tissue development inside BMS has only been reported recently.

Limitations
The number of patients studied was small and only those with recurrent ischaemic symptoms were studied. However, we selected only those with stent implantation at least 4 years ago to evaluate late changes inside the stent. Since we did not perform directional atherectomy or other intravascular modalities, a direct comparison of OCT findings with histology or other images was impossible. Instead, we used the validated OCT criteria for plaque characterisation. Finally, the in vivo detection of macrophage is not fully validated and requires caution for interpretation.

CONCLUSIONS
LRP with a thin fibrous cap was observed inside previous BMS at late follow-up in patients with recurrent ischaemia. Disruption of LRP inside the previous stent may be one possible mechanism for VLST.

Competing interests SZ is an employee of LightLab Imaging; IKJ received research grant from LightLab Imaging.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the IRB of the 2nd affiliated hospital of Harbin Medical University.

Contributors JH, IKJ and BY designed the study, analysed the data, drafted and revised the manuscript. BY give the final approval for the manuscript submitted. The other authors took part in the collection and analysis of the data.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

Table 3 Comparison of baseline characteristics between patients with and without in-stent, lipid-rich plaque

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with in-stent, lipid-rich plaque (n=16)</th>
<th>Patients without in-stent, lipid-rich plaque (n=23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up period, (years)</td>
<td>6.63±1.38</td>
<td>6.47±1.20</td>
<td>0.752</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.1±7.5</td>
<td>60.1±10.5</td>
<td>0.357</td>
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<tr>
<td>Male, n (%)</td>
<td>14 (87.5)</td>
<td>16 (69.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>13 (81.3)</td>
<td>9 (39.1)</td>
<td>0.139</td>
</tr>
<tr>
<td>Diabetics, n (%)</td>
<td>4 (25)</td>
<td>1 (4.3)</td>
<td>0.027</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>9 (56.3)</td>
<td>5 (21.7)</td>
<td>0.464</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>13 (81.3)</td>
<td>15 (65.2)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

Figure 2 Optical coherence tomography image for a disrupted fibrous cap (white arrow) of in-stent lipid-rich plaque with thrombus (green arrow) 5 years after implantation in the right coronary artery.

Figure 3 Optical coherence tomography image of macrophage infiltrations (bands of high reflectivity with shadow behind) (white arrow) in the fibrous cap of lipid-rich plaque inside the previous stent.

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Interventional cardiology


Images in cardiology

Power Doppler three-dimensional visualisation of aortic arch interruption in fetal life

A 29-year-old lady was referred for fetal cardiac assessment at the 23rd week of gestation after concern regarding an abnormal four-chamber view and the suggestion of a ventricular septal defect. Detailed fetal echocardiography using standard greyscale imaging and colour Doppler technique confirmed the presence of a large perimembranous ventricular septal defect and suggested the presence of an interruption of the aortic arch between the left common carotid and left subclavian artery.

The use of power Doppler imaging, where the amplitude of the signal is encoded in contrast to the frequency, at both 23 and 29 of 40 weeks, allowed for three-dimensional reconstruction of the interrupted arch (panel A). Power Doppler imaging shows benefit over colour Doppler imaging in the assessment of an aortic arch pathological condition, as it confers better edge definition and angle independence, allowing for the assessment of low velocity flow, perpendicular to the ultrasound beam (panel B). This angle independence is a key advantage over standard techniques, particularly in fetal echo assessments, where limited positioning compromises assessments of flow and representation of vascular structures.

This three-dimensional visualisation allowed for better parental understanding during prenatal counselling and facilitated surgical planning.

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Competing interests None.

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