Impact of Coronary Stent Fracture on Restenotic Neointimal Tissue Characterization After Drug-Eluting Stent Implantation
An Integrated Backscatter Intravascular Ultrasound Study

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Summary
Although drug-eluting stents (DESs) reduce the rates of in-stent restenosis (ISR) and subsequent target lesion revascularization, stent fracture (SF) after DES implantation has become an important concern because of its potential association with restenosis and stent thrombosis. We aimed to assess the pathogenic impact of SF on in-stent restenotic neointimal tissue components after DES implantation. We analyzed 43 consecutive patients (14 with SF and 29 without SF) with ISR requiring revascularization after DES implantation between January 2008 and March 2014. For evaluation of in-stent tissue components, integrated backscatter intravascular ultrasound (IB-IVUS) was performed. SF was defined as complete or partial separation of stent segments observed using plain fluoroscopy or intravascular ultrasound. On volumetric IB-IVUS analyses, patients with SF had a significantly higher percentage of lipid tissue volume within the neointima and a significantly lower percentage of fibrous tissue volume than those without (37.3 ± 18.9% versus 24.9 ± 12.4%, P = 0.02, and 61.2 ± 18.3 versus 72.6 ± 12.1%, P = 0.04, respectively). Moreover, SF was positively correlated with the percentage of lipid volume on multiple linear regression analysis after adjustment for confounding factors (β = 0.36, P = 0.03). In conclusion, SF is associated with larger lipid tissue volume within the neointima after DES placement, suggesting a contribution to the development of neoatherosclerosis and vulnerable neointima. Thus SF might lead to future adverse coronary events.

Key words: Restenosis, Neoatherosclerosis

Although drug-eluting stents (DESs) have radically reduced the rates of in-stent restenosis (ISR) and subsequent target lesion revascularization compared with bare-metal stents, widespread use of DES has given rise to several unresolved important issues. Particularly, concerns about late stent thrombosis, very late thrombosis, and late catch-up phenomenon have been raised. Recently, several reports documented the development of neoatherosclerosis inside DES, suggesting a potential impact on late complications after stent implantation. In particular, stent fracture (SF) after DES implantation has recently become an important problem because of its potential association with ISR, target lesion revascularization, and stent thrombosis. However, the influence of SF on restenotic neointimal tissue characterization after DES implantation has not been fully evaluated.

Integrated backscatter intravascular ultrasound (IB-IVUS) allows tissue characterization of coronary plaques, with excellent correlation with histological findings. Lipid-rich plaques assessed by IB-IVUS have been associated with an increased risk of adverse coronary events, including acute coronary syndrome. Accordingly, we here investigated the relationship between SF and in-stent restenotic neointimal tissue components after DES implantation using IB-IVUS.

Methods

Patients, study design, and definition: From January 2008 to August 2014, we prospectively recruited patients with ISR requiring percutaneous coronary intervention (PCI) after DES implantation at Yokkaichi Municipal Hospital. ISR was defined as diameter stenosis ≥50% within the stented segment by coronary angiography. All patients

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SF was defined as complete or partial separation of stent segments observed using plain fluoroscopy without contrast injection or IVUS. SF was classified as grade I to V: I = involving a single-strut fracture; II = 2 or more strut fractures without deformation; III = 2 or more strut fractures with deformation; IV = multiple strut fractures with acquired transection but without a gap; and V = multiple strut fractures with acquired transection with a gap in the stent body. Angiographic diagnosis of SF required an independent view and the agreement of 2 independent cardiologists. Diagnosis of SF by IVUS was based on a careful review of the IVUS images and the agreement of 2 independent cardiologists. Acute coronary syndrome included acute myocardial infarction and unstable angina pectoris. The former was diagnosed by an elevation in at least one positive cardiac biomarker (creatine kinase, creatine kinase-MB, or troponin), distinctive electrocardiogram changes, and continuous acute chest pain. The latter was diagnosed by angina with progressive chest pain or an increase in cardiac enzyme markers (e.g., creatine kinase-MB, troponin), ECG changes, and continuous acute chest pain.

The transducer was advanced to the distal reference lesion, and then automated pullback was performed to the proximal reference lesion through the stent lesion. All in-stent segments were assessed at an axial interval of 1 mm. Conventional 2-dimensional IVUS image analysis was conducted for lumen cross-sectional area (CSA), stent CSA, and neointimal CSA (neointimal tissue area = stent CSA — lumen CSA) using the software of the IVUS system. A two-dimensional IVUS measurement was performed at the site of the minimum lumen area and SF. Conventional 3-dimensional images were obtained with reference to the sum of stent CSA, lumen CSA, and neointimal CSA at an axial interval of 1 mm for the segments analyzed, along with the stented lesion volume, lumen volume, and total neointimal volume.

IB signals were acquired using a personal computer equipped with custom software connected to an IVUS imaging system to obtain radio frequency signal trigger output. US backscattered signals were generated with a 40-MHz mechanically rotating IVUS catheter (Atlantis SR Pro; Boston Scientific), motorized catheter pullback (0.5 mm/second), and custom software (IB-IVUS, YD Company, Ltd., Nara, Japan), between January 2008 and November 2010. However, the original IB-IVUS system was then updated to the VISIWAY system (Terumo, Tokyo, Japan), and this was used with a 40-MHz mechanically rotating IVUS catheter (ViewIT; Terumo, Tokyo, Japan), motorized catheter pullback (0.5 mm/second), and custom software (VISIATLAS; Terumo, Tokyo, Japan), between December 2010 and August 2014. Conventional IVUS measurements were performed according to the standards laid out by the American College of Cardiology and the European Society of Cardiology. The transducer was advanced to the distal reference lesion, and then automated pullback was performed to the proximal reference lesion through the stent lesion. All in-stent segments were assessed at an axial interval of 1 mm. Conventional 2-dimensional IVUS image analysis was conducted for lumen cross-sectional area (CSA), stent CSA, and neointimal CSA (neointimal CSA = stent CSA — lumen CSA) using the software of the IVUS system. A two-dimensional IVUS measurement was performed at the site of the minimum lumen area and SF. Conventional 3-dimensional images were obtained with reference to the sum of stent CSA, lumen CSA, and neointimal CSA at an axial interval of 1 mm for the segments analyzed, along with the stented lesion volume, lumen volume, and total neointimal volume.
Figure 2. A: Plain fluoroscopy without contrast injection, coronary angiography, and serial conventional IVUS and IB-IVUS images from patients with grade III SF (percentage of lipid volume and fibrous volume 49.5% and 49.2%, respectively). Partial stent struts separation with deformation was confirmed (arrow head). B: Plain fluoroscopy without contrast injection, coronary angiography, and serial conventional IVUS and IB-IVUS images from patients without SF (percentage of lipid volume and fibrous volume 17.4% and 80.9%, respectively).

Table I. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SF (n = 14)</th>
<th>non SF (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.9 ± 5.4</td>
<td>72.3 ± 7.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Male</td>
<td>10 (71%)</td>
<td>26 (90%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.9 ± 2.9</td>
<td>23.7 ± 2.8</td>
<td>0.40</td>
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<tr>
<td>Hypertension</td>
<td>8 (57%)</td>
<td>24 (83%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (79%)</td>
<td>18 (62%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (36%)</td>
<td>19 (66%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3 (21%)</td>
<td>6 (21%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate</td>
<td>58.4 ± 24.3</td>
<td>53.4 ± 31.6</td>
<td>0.59</td>
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<tr>
<td>Lipid profiles, at initial PCI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High-density lipoprotein cholesterol, mg/dL</td>
<td>57.0 ± 18.8</td>
<td>49.7 ± 11.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
<td>138.0 ± 39.0</td>
<td>112.5 ± 24.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>111.6 ± 62.8</td>
<td>116.8 ± 54.4</td>
<td>0.64</td>
</tr>
<tr>
<td>Lipid profiles, at PCI for ISR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mg/dL</td>
<td>57.3 ± 17.1</td>
<td>51.8 ± 7.9</td>
<td>0.25</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
<td>103.6 ± 22.8</td>
<td>97.8 ± 22.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>137.9 ± 70.8</td>
<td>131.3 ± 53.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Stent implantation for acute coronary syndrome</td>
<td>6 (43%)</td>
<td>8 (28%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Clinical presentation of restenosis</td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Stable angina</td>
<td>10 (71%)</td>
<td>23 (79%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>4 (29%)</td>
<td>6 (21%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Interval from stent implantation, months</td>
<td>47.0 ± 28.7</td>
<td>37.7 ± 33.3</td>
<td>0.39</td>
</tr>
<tr>
<td>Medications (when ISR was identified)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>14 (100)</td>
<td>29 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>11 (79%)</td>
<td>21 (72%)</td>
<td>0.95</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>7 (50%)</td>
<td>20 (69%)</td>
<td>0.38</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>5 (36%)</td>
<td>9 (31%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Statin</td>
<td>12 (86%)</td>
<td>19 (66%)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). SF indicates stent fracture; PCI, percutaneous coronary intervention; ISR, in-stent restenosis; ACEI, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

percentage of fibrous tissue area (fibrous tissue area/ neointima area), and the percentage of lipid tissue area (lipid tissue area/neointima area) were automatically generated by the IB-IVUS system. The volume percentages of calcified (calcified tissue volume/neointima volume), fibrous (fibrous tissue volume/neointima volume), and lipid tissue (lipid tissue volume/neointima volume) were also acquired. Each neointimal component was calculated with the sum of calcified, fibrous, and lipid tissue areas in each CSA at 1-mm axial intervals for the segments analyzed.
Ohota et al. demonstrated grayscale IVUS and IB-IVUS data to be directly comparable between Boston Scientific’s and Terumo’s systems so that both are in line with the gold standard of histology for plaque constituents. 22) Representative cases are shown in Figure 2.

**Statistical analyses:** Statistical analyses were performed with the SPSS software (Statistical Package for the Social Sciences), program version 18 (SPSS, Chicago, IL, USA). Categorical variables between SF and non-SF groups were compared with χ² or Fisher’s exact tests and continuous variables with the Student’s t-test. Simple linear regression analysis was performed to assess the relationship between percent lipid and fibrous tissue volume, and various parameters. Multiple linear regression analysis was conducted with adjustment for the interval from stent implantation, 26 and the variables with a P-value < 0.20 on simple linear regression analysis. Statistical significance was defined as a P-value < 0.05.

**Results**

**Baseline patient characteristics:** Of the 43 patients, SF was observed in 14 (32.6%). The baseline clinical characteristics of SF and non-SF groups are summarized in Table I. There were no differences in age, sex, coronary risk factors, lipid profiles, clinical presentation of ISR, and medications when ISR was identified between the two groups. Also, the interval periods from DES implantation were similar (47.0 ± 28.7 versus 37.7 ± 33.3 months; P = 0.39).

**Characteristics of ISR:** ISR characteristics are detailed in Table II. No significant differences were detected in lesion location, quantitative coronary angiography analysis, and restenosis patterns between the two groups. However, patients with SF tended to have undergone PCI using sirolimus-eluting stents more frequently. Besides, the SF group showed significantly longer total stent lengths and greater numbers of implanted stents than the non-SF group (37.9 ± 13.8 versus 23.9 ± 13.6 mm; P = 0.005, 1.7 ± 0.9 versus 1.2 ± 0.4; P = 0.048, respectively).

**In-stent restenotic tissue characterization:** Table III summarizes data about cross-sectional and volumetric tissue characterization of in-stent neointima assessed by conventional IVUS and IB-IVUS. The intra- and inter-observer variabilities of the percent lipid and fibrous tissue volumes were well correlated [r = 0.91 (P < 0.01) and r = 0.90 (P < 0.01), r = 0.88 (P < 0.01) and r = 0.86 (P < 0.01), respectively]. In the 2-dimensional IB-IVUS analysis, the percent lipid tissue area was significantly larger and the percent fibrous tissue area was significantly smaller in the SF group than in the non-SF group (37.2 ± 20.3% versus 23.0 ± 13.5%, P = 0.01; and 61.2 ± 19.8% versus 74.4 ± 12.7%, P = 0.02, respectively). Also, neointima at the site of SF was rich in lipid tissue in the SF group. Similarly, in the volumetric analysis, the lipid tissue volume in the SF group was significantly greater than in the non-SF group and the fibrous tissue volume was significantly less (37.3 ± 18.9% versus 24.9 ± 12.4%, P =
The incidence of SF in the clinical setting has been reported to be about 1-8%.24 25 Several studies have demonstrated that sirolimus-eluting stents are more likely to cause SF because of the closed-cell design and the stainless steel material with low flexibility and conformability.25 Furthermore, it has been reported that overlap stenting for tortuous or hinged lesions continue to pay attention to SF in case of longer or over-lapping stenting for tortuous or hinged lesions.

SF has been associated with higher potential risks of ISR, target lesion revascularization, and stent thrombosis.14 Although it is not fully understood why SF causes adverse coronary events, the mechanisms are probably related to lower drug delivery at the fracture site and higher mechanical irritation by the fractured struts, causing smooth muscle cell proliferation, and impaired re-endothelialization. In addition to these factors, in-stent neoatherosclerotic development might be a mechanism of 0.02; and 61.2 ± 18.3% versus 72.6 ± 12.1%, \( P = 0.04 \), respectively).

Results of simple and multiple linear regression analyses are shown in Table IV, V. On simple linear regression analysis, the presence of SF had a significant positive correlation with the percentage of lipid volume and a negative correlation with the percentage of fibrous volume within in-stent neointimal tissue (\( r = 0.38, P = 0.02 \); and \( r = -0.33, P = 0.04 \), respectively). After adjusting for confounding factors, SF was positively correlated with the percentage of lipid tissue volume and negatively correlated with the fibrous tissue volume (\( \beta = 0.36, P = 0.03; \) and \( \beta = -0.32, P = 0.047 \), respectively).

**Discussion**

The major findings of the present study are as follows: (1) after DES implantation, patients with SF had a significantly greater percent lipid volume in the restenotic neointimal tissue and a significantly lower percent fibrous volume based on conventional IVUS and IB-IVUS analyses; and (2) patients with SF had significantly longer total stent lengths and greater numbers of implanted stents during the previous PCI.

The incidence of SF in the clinical setting has been reported to be about 1-8%.14-25 Several studies have demonstrated that sirolimus-eluting stents are more likely to cause SF because of the closed-cell design and the stainless steel material with low flexibility and conformability.25 Furthermore, it has been reported that overlap stenting and longer stent length are associated with SF.25 Concordant with previous studies, our patients with SF had undergone PCI using longer and a greater number of stents compared with those without. Moreover, the rate of sirolimus-eluting stent use tended to be higher in the SF group. At present, we mainly use second-generation DES. Although, compared with sirolimus-eluting stents, the rates of SF after second-generation DES implantation are relatively low, SF still occurs.10,25-27 Therefore, we must continue to pay attention to SF in case of longer or overlapping stenting for tortuous or hinged lesions.

SF has been associated with higher potential risks of ISR, target lesion revascularization, and stent thrombosis.13 Although it is not fully understood why SF causes adverse coronary events, the mechanisms are probably related to lower drug delivery at the fracture site and higher mechanical irritation by the fractured struts, causing smooth muscle cell proliferation, and impaired re-endothelialization. In addition to these factors, in-stent neoatherosclerotic development might be a mechanism of...
late coronary events including stent thrombosis. According to a previous study, adverse pathologic findings such as stent thrombosis and restenosis at the fracture sites were really observed in SF with grade IV and V. Despite the lower grades of SF observed in our study, the stent struts at the fracture site are continuous stress to arterial intima and induce inflammation. Thus, SF might lead to in-stent neointimal neoatherosclerosis.

A recent histopathology study by Nakazawa et al. demonstrated a higher incidence of neoatherosclerotic change linearly with time course after DES implantation. The correlation between the interval from stent implantation and lipid or fibrous tissue volume in this study is not contradictory with the previous study. However, because of the small number, statistical significance was not apparent in our study. Furthermore, it should be noted that the median duration from stent implantation in their study was 361 days (172-540 days, interquartile range), in contrast to our 848 days (322-2,148 days, interquartile range). Since longer stent implant duration has also been identified as an independent risk factor for SF, this difference could clearly have influenced the results.

To the best of our knowledge, this is the first report that showed the impact of SF on in-stent restenotic neointimal tissue characterization. We should be careful about the incidence of neoatherosclerosis and adverse coronary events, including ST, for patients with SF.

**Study limitations:** This study has several limitations. First, only 43 patients were involved from a single center. For this reason, the possibility of selection bias and low statistical power must be considered. Second, we used two different kinds of conventional IVUS and IB-IVUS systems. Although this might influence the results, it has been proven that data with these two systems were essentially comparable. Third, we analyzed only the neointima requiring target lesion revascularization rather than stable neointimal tissue. Fourth, IB-IVUS was initially validated for the atherosclerosis of native coronary arteries, not for the neointima within stented segments. Further validation assessments may therefore be required.

**Conclusions**

SF is associated with a larger lipid tissue volume within the neointima after DES placement, suggesting a contribution to the development of neoatherosclerosis and vulnerable neointima. Thus, SF might lead to future adverse coronary events including restenosis, target vessel revascularization, stent thrombosis, and late catch-up phenomenon.

**Disclosures**

**Conflicts of interest:** The authors do not have any potential conflicts of interest associated with this study.

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