Incidence, Risk Factors, and Clinical Sequelae of Angiographic Peri-Stent Contrast Staining After Sirolimus-Eluting Stent Implantation

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Background—We have noted abnormal angiographic findings—at the sites of drug-eluting stent implantation, suggesting contrast staining outside the stent struts—that do not fulfill the classic definition of coronary artery aneurysm. We propose a new term, peri-stent contrast staining (PSS), for these abnormal angiographic findings and assess their incidence, risk factors, and clinical sequelae.

Methods and Results—Peri-stent contrast staining was defined as contrast staining outside the stent contour extending to ≥20% of the stent diameter. The study population consisted of 3081 lesions (1998 patients) that were treated exclusively with sirolimus-eluting stents and were evaluated by follow-up angiography within 12 months after sirolimus-eluting stent implantation in a single center. Late acquired PSS was observed in 58 lesions (1.9%) in 49 patients (2.5%). Independent risk factors of PSS included chronic total occlusion, whereas negative risk factors for PSS were left circumflex coronary artery lesion and in-stent restenosis lesion. Stent fracture was more frequently observed in lesions with PSS than in lesions without PSS (43.1% versus 5.4%, P < 0.0001). Excluding 269 lesions with target-lesion revascularization within 12 months, the study population for long-term follow-up consisted of 51 lesions (42 patients) with PSS and 2761 lesions (1751 patients) without PSS. Cumulative incidence of target-lesion revascularization and definite very late stent thrombosis at 3 years in the PSS group was higher than that in the non-PSS group (15.0% versus 6.5%, and 8.2% versus 0.2%, respectively).

Conclusions—Peri-stent contrast staining found within 12 months after sirolimus-eluting stent implantation appeared to be associated with subsequent target-lesion revascularization and very late stent thrombosis. (Circulation. 2011;123:2382-2391.)

Key Words: thrombosis • stents • restenosis • coronary disease

Drug-eluting stents (DES) dramatically inhibit neointimal proliferation, thereby significantly reducing the need for target-lesion revascularization (TLR)1,2; however, concerns have been raised about the long-term safety of DES.3,4 Late adverse events occurring beyond 1 year after stent implantation, very late stent thrombosis (VLST) in particular, have been reported to be more prevalent after DES implantation than after bare-metal stent implantation.5,6 Although the mechanisms of VLST are currently very poorly understood, several human autopsy series have suggested a possible relationship between VLST and abnormal vessel wall pathology, including profound inflammatory responses and de novo atherosclerosis formation.7–9 Abnormal vessel wall responses after DES implantation also have been demonstrated by in vivo human studies using intravascular ultrasound (IVUS). In several IVUS studies, late acquired incomplete stent apposition (ISA) with positive remodeling was reported to be seen in 5% to 13% of lesions treated with sirolimus-eluting stents (SES), whereas it was rarely seen in lesions treated with bare-metal stents.10–12 An association between late-acquired ISA and VLST has been suggested by several IVUS studies demonstrating very high prevalence (73% to 77%) of ISA in the setting of VLST.13–15 Furthermore, abnormal vessel wall responses manifesting as aneurysm formation also were demonstrated by coronary angiography after DES implantation in several case reports.16,17 Recently, in a systematic

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evaluation of coronary artery aneurysms (CAA), defined as a localized angiographic dilatation of the vessel lumen (50% larger than the adjacent reference vessel) at the site of DES implantation, Alfonso et al identified CAA in 15 patients (1.3%) out of 1197 consecutive patients; 3 patients suffered from VLST at the time of CAA diagnosis or during follow-up thereafter. In our clinical practice, we have noted abnormal angiographic findings—at the site of DES implantation, suggesting contrast staining outside the stent struts—that do not fulfill the definition of CAA, and therefore propose to call this finding peri-stent contrast staining (PSS).

In the current study, we retrospectively evaluated the incidence and risk factors for PSS, as well as the inter- and intra-observer variability for diagnosis of PSS in a large number of patients who underwent SES implantation at a single center in Japan. Also, incidence of VLST and TLR beyond 1 year after SES implantation was compared between those lesions either with or without a diagnosis of PSS within 12 months after SES implantation.

Methods

Study Population
From November 2002 through December 2006, 12 243 lesions in 6363 patients were treated with percutaneous coronary intervention (PCI), and 3669 lesions in 2285 patients were exclusively treated with SES, at Kurashiki Central Hospital. Among 3669 lesions treated exclusively by SES, angiographic follow-up study within 12 months after PCI was performed in 3081 lesions (85.4%). The current study population consisted of 3081 lesions (1998 patients) that were treated exclusively with SES and were evaluated by at least 1 follow-up angiographic study within 12 months after SES implantation. Excluding 269 lesions that underwent TLR, including those TLR for stent thrombosis (ST) within 12 months after SES implantation, 2812 lesions in 1793 patients constituted the study population for long-term clinical follow-up. In the latter study population, the incidence of VLST and TLR beyond 1 year after SES implantation was compared between the 2 groups of lesions either with or without a diagnosis of PSS at follow-up angiographic study within 12 months (Figure 1). Analyses were made on a lesion basis. All-cause death was evaluated on a patient basis.

Recommended antiplatelet regimen after SES implantation was aspirin (81 mg daily) indefinitely and thienopyridine (200 mg ticlopidine or 75 mg clopidogrel daily) for at least 3 months. Duration of dual antiplatelet therapy was left to the discretion of each attending physician. Stringent adherence to continued dual antiplatelet therapy was recommended when PSS was found at time of follow-up angiography.

This study was an investigator-driven initiative. The study protocol was approved by the institutional review board of Kurashiki Central Hospital. Because of retrospective enrollment, written informed consents from the patients were waived. This strategy is in accordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare of Japan.

Qualitative and Quantitative Angiographic Analysis

Follow-up coronary angiographic study was scheduled at 8 months and 20 months after PCI according to the local site protocol. In cases in which the target lesions were chronic total occlusions (CTOs) or were located in the left main coronary artery, follow-up coronary angiographic study also was scheduled at 3 months after PCI. Some patients in this study population underwent multiple angiographic studies within 12 months after stent implantation. For lesions with documented PSS within 12 months after stent implantation, the first angiographic study performed was regarded as the index coronary angiographic study. For lesions without documented PSS within 12 months after stent implantation, the first angiographic study performed was regarded as the index coronary angiographic study.

Clinical Perspective on p 2391

In the current study, we retrospectively evaluated the incidence and risk factors for PSS, as well as the inter- and intra-observer variability for diagnosis of PSS in a large number of patients who underwent SES implantation at a single center in Japan. Also, incidence of VLST and TLR beyond 1 year after SES implantation was compared between those lesions either with or without a diagnosis of PSS within 12 months after SES implantation.
quantitative angiographic analysis was performed through the int-
sten segment and the adjacent proximal and distal 5-mm vessel
segment. Quantitative measurements included reference vessel di-
ameter, minimal luminal diameter, percentage diameter stenosis, and
lesion length. Restenosis was defined as ≥50% diameter stenosis at
follow-up. To assess interobserver variability for the diagnosis of PSS, the
angiograms were analyzed independently by 2 experienced interven-
tional cardiologists who were blinded to the clinical and procedural
data. Furthermore, 1 of the 2 observers evaluated all the angiograms
again at 6 months after initial evaluation to assess intraobserver
variability for the diagnosis of PSS. The observer was unaware of the
results of the previous evaluation. The degree of agreement for inter-
and intraobserver variability was evaluated by applying the κ
statistics. In case of disagreement, the decision of a third observer
was obtained and the final decision on the diagnosis of PSS was
made by consensus.

**Definition and Morphological Classification of Peri-Stent Contrast Staining**

The definition and morphological classification of PSS was deter-
mained according to the consensus of 5 experienced interventional
cardiologists, including 2 physicians outside Kurashiki Central
Hospital. Peri-stent contrast staining was defined as contrast staining
outside the stent contour extending to ≥20% of the stent diameter,
measured by quantitative coronary angiography. Severe PSS was
defined as contrast staining outside the stent contour extending to
≥50% of the stent diameter. Morphological classification of PSS
included monofocal, multifocal, segmental with irregular contour,
and segmental with smooth contour (Figure 2). Timing of PSS was
classified as resolved PSS (PSS observed at poststenting but not at
follow-up), persistent PSS (PSS observed both at poststenting and
follow-up), and late acquired PSS (PSS observed at follow-up but
not at poststenting).

**Clinical Follow-Up**

Follow-up information until May 2010 was collected by the clinical
research coordinators at Kurashiki Central Hospital, either from
hospital charts or by contacting patients and/or referring physicians.
Target-lesion revascularization and ST events were adjudicated by the
consensus of 2 interventional cardiologists in the hospital.
Lesions that underwent TLR within 12 months after the initial SES
implantation were excluded for the long-term follow-up study. The
follow-up interval was calculated on the basis of the day of the index
angiographic follow-up study.

Target-lesion revascularization was defined as retreatment (either
by PCI or coronary artery bypass grafting surgery) for a significant
lesion within the stented segment or within 5 mm of the stent borders
cau sed by restenosis or ST of the target lesion. There was no
distinction between whether TLR was clinically or angiographically
driven. Stent thrombosis was defined as definite ST according to the
Academic Research Consortium definition.

**Statistical Analysis**

Data are presented as values and percentages, mean±SD, or median
and first and third quarter (Q1 and Q3). Categorical variables were
compared between groups with the χ² test or the Fisher exact test.
Continuous variables were compared between groups using the
Student t test or the Wilcoxon rank sum test, based on the
distribution. Multivariable logistic regression analysis with a random
effect on the patient was used for the lesion-based analysis of the risk
factors for PSS. A multivariable regression model was constructed
using PSS within 12 months after SES implantation as a dependent
variable and 6 baseline variables with P<0.05 in the univariate
analysis as potential independent variables. Potential independent
variables included right coronary artery, left circumflex coronary
artery, CTO, in-stent restenosis, reference diameter, and lesion
length. Continuous variables were dichotomized by clinically mean-
ingful reference value or median value.

Cumulative incidence of TLR, ST, and death after diagnosis of
PSS was estimated by the Kaplan-Meier method. Because of the
small numbers of events in the PSS group, statistical comparisons
were not conducted for the cumulative event rates.

P<0.05 was considered statistically significant. All statistical tests
were 2-tailed. All statistical analyses were conducted by a physician...
Table 1. Baseline Patient Characteristics

|                          | Entire Cohort | PSS (+) | PSS (-) | P  
|--------------------------|---------------|---------|---------|-----
| Patients, n              | 1998          | 49      | 1949    |     
| Male sex                 |               |         |         |     
| Age, y                   | 1528 (76)     | 37 (76) | 1491 (77) | 0.87
| Acute coronary syndrome  | 314 (16)      | 4 (8.2) | 310 (16) | 0.17
| History of myocardial infarction | 861 (43) | 23 (48) | 838 (44) | 0.56
| Extent of coronary artery disease |         |         |         | 0.66

| Single-vessel disease    | 1068 (53)     | 28 (57) | 1040 (53) |     
| Double-vessel disease    | 539 (27)      | 12 (24) | 527 (27) |     
| Triple-vessel disease    | 221 (11)      | 6 (12)  | 215 (11) |     
| Left main disease        | 170 (9)       | 3 (6.1) | 167 (8.6) |     
| Diabetes mellitus        | 834 (42)      | 16 (33) | 818 (42) | 0.19
| Insulin treated          | 251 (13)      | 3 (6.1) | 248 (13) | 0.27
| Hypertension             | 1398 (70)     | 33 (67) | 1365 (70) |     
| Hypercholesterolemia     | 1004 (50)     | 25 (51) | 979 (51) | 1.0
| Hemodialysis             | 88 (4.4)      | 2 (4.1) | 86 (4.4) | 1.0

Categorical variables are expressed as n (%); continuous variables as mean±SD. PSS (+) indicates the presence of peri-stent contrast staining; PSS (−), the absence of peri-stent contrast staining.

(M.I.) and by an independent statistician (T.M.) with the use of JMP 8.0.2 (SAS Institute Inc, Cary, NC) and SAS 9.2 (SAS Institute).

Results

Baseline Clinical and Angiographic Characteristics

In the current study population, the prevalence of patients with complex characteristics such as diabetes mellitus, hemodialysis, and CTO was high, whereas the prevalence of culprit lesions for AMI was low (Tables 1 and 2).

Incidence, Morphological Pattern, and Time Course of Peri-Stent Contrast Staining

Peri-stent contrast staining was present in 4 lesions at poststenting, including 1 lesion with resolved PSS and 3 lesions with persistent PSS. Late acquired PSS within 12 months after the initial SES implantation was observed in 51 lesions (88%) with median interval of 159 (Q1 to Q3: 97 to 245) days and 243 [Q1 to Q3: 100 to 247] days, P<0.0001. Severe PSS was seen only in 7 lesions (12%). In 35 patients with PSS in whom multiple lesions were treated with SES, PSS was present in multiple lesions in 5 patients (14%). Morphonologically, segmental types of PSS were predominant, with almost equal distribution of irregular-contour and smooth-contour subtypes (Table 3). Examination by IVUS and optical coherence tomography (OCT) confirmed the presence of ISA in a lesion with PSS (Figure 3A). Stent fracture was observed significantly more frequently in lesions with PSS than in lesions without PSS (43.1% versus 5.4%, P<0.0001).

Reference vessel diameter and minimal luminal diameter at the time of the index follow-up angiography were significantly greater in the PSS group than in the non-PSS group (3.32±0.51 mm versus 3.05±0.55 mm, P=0.0004, and 2.57±0.57 mm versus 2.34±0.65 mm, P=0.01, respectively). Percentage diameter stenosis was similar between the 2 groups (22.1±12.5% versus 23.4±12.6%, P=0.59).

Among 58 lesions with documented PSS at the time of the index follow-up angiographic study, subsequent follow-up angiographic study without intercurrent TLR was performed in 51 lesions (88%) with median interval of 159 (Q1 to Q3: 153 to 362) days from the index follow-up angiographic study.

Table 2. Baseline Lesion Characteristics

|                          | Entire Cohort | PSS (+) | PSS (-) |     
|--------------------------|---------------|---------|---------|-----
| Lesions, n               | 3081          | 58      | 3023    |     
| ACC/AHA lesion classification |               |         |         |     
| Type A                   | 100 (3.2)     | 1 (1.7) | 99 (3.3) |     
| Type B1                  | 341 (11)      | 5 (8.6) | 336 (11) |     
| Type B2                  | 1404 (46)     | 10 (17) | 1394 (46) |     
| Type C                   | 1152 (37)     | 41 (71) | 1111 (37) |     
| Culprit for acute myocardial infarction | 55 (1.8) | 0 | 55 (1.8) |     
| RCA                      | 1185 (38)     | 30 (52) | 1155 (38) |     
| LAD                      | 1037 (34)     | 21 (36) | 1016 (34) |     
| LCX                      | 643 (21)      | 5 (8.6) | 638 (21) |     
| LMCA                     | 138 (4.5)     | 0      | 138 (4.6) |     
| In-stent restenosis      | 491 (16)      | 2 (3.9) | 489 (16) |     
| Aorto-ostial lesion      | 294 (9.5)     | 2 (3.5) | 292 (9.7) |     
| CTO                      | 372 (12)      | 20 (35) | 352 (12) |     
| Bifurcation              | 894 (29)      | 18 (32) | 876 (30) |     
| Severely angulated (90°<) | 23 (0.8)      | 2 (3.5) | 21 (0.7) |     
| Severe calcification     | 338 (11)      | 10 (18) | 328 (11) |     
| Reference diameter       | 2.88±0.47     | 3.1±0.45 | 2.87±0.47 |     
| preprocedure, mm         |               |         |         |     
| Minimal luminal diameter | 0.84±0.56     | 0.6±0.62 | 0.85±0.56 |     
| preprocedure, mm         |               |         |         |     
| Diameter stenosis        | 70±18         | 81±19   | 70±18   |     
| preprocedure, %          |               |         |         |     
| Lesion length, mm        | 20±12         | 29±21   | 19±11   |     
| Maximum balloon pressure | 18±4          | 19.6±4  | 18±4    |     
| atm                      |               |         |         |     
| Maximum balloon size, mm | 3.0±0.4       | 3.1±0.4 | 3.0±0.4 |     
| Number of stents used    | 1.3±0.6       | 1.7±0.8 | 1.3±0.6 |     

Categorical variables are expressed as n (%); continuous variables as mean±SD. PSS (+) indicates the presence of peri-stent contrast staining; PSS (−), the absence of peri-stent contrast staining.

Table 3. Morphologic Classification of PSS

<table>
<thead>
<tr>
<th>PSS Morphology</th>
<th>Number of Lesions (Proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monofocal</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Segmental irregular-contour</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Segmental smooth-contour</td>
<td>23 (40)</td>
</tr>
</tbody>
</table>

PSS indicates peri-stent contrast staining.
Progression in terms of the severity of PSS was seen in 23 lesions (45%), whereas regression was seen in 13 lesions (25%). Among 3023 lesions without diagnosis of PSS at the time of the index follow-up angiographic study, subsequent follow-up angiographic study without intercurrent TLR was performed in 2438 lesions (81%) with median interval of 364 (Q1 to Q3: 158 to 369) days, and PSS was newly diagnosed only in 9 lesions (0.4%).

Inter- and Intraobserver Variability for Diagnosis of Peri-Stent Contrast Staining
For the interobserver variability analysis, PSS was judged to be present by the first observer, but not by the second observer in 5 lesions. For the intraobserver variability analysis, PSS was judged to be present at the initial evaluation, but not at the second evaluation in 2 lesions. \( \kappa \) Values for inter- and intraobserver variability were 0.96 and 0.98, respectively, suggesting an almost perfect degree of agreement.

Risk Factors of Peri-Stent Contrast Staining
Baseline patient characteristics were generally similar between the 2 groups of patients with or without PSS. However, patients with PSS tended to be younger and tended to have diabetes mellitus less frequently (Table 1). Baseline lesion characteristics were significantly different between the 2 groups in several aspects. Lesions with PSS more often were American Heart Association/American College of Cardiology type C and CTOs and less often in-stent restenosis. Lesions with PSS were more often located in the right coronary artery and less often in the left circumflex coronary artery. Also, lesions with PSS had significantly larger reference vessel diameter, smaller minimal luminal diameter preindex procedure, and longer lesion length. Procedures in the PSS group were characterized by use of higher inflation pressure, bigger balloon size, and use of a greater number of stents (Table 2). The independent risk factor for PSS identified by the multivariable logistic regression analysis was CTO whereas negative risk factors for PSS were left circumflex coronary artery lesion and in-stent restenosis lesion (Table 4).

Clinical Sequelae: Peri-Stent Contrast Staining Group Versus Non-Peri-Stent Contrast Staining Group
The index follow-up angiographic study revealed restenosis in 3 lesions (5.7%) in the PSS group, and in 217 lesions (7.4%) in the non-PSS group, respectively \( (P=0.61) \). Based on the finding at the time of the index follow-up angiographic study, TLR was performed in 4 lesions (6.9%) in the PSS group, and in 175 lesions (5.8%) in the non-PSS group, respectively \( (P=0.73) \). Early TLR within the first year tended

<table>
<thead>
<tr>
<th>Variables</th>
<th>Present:Lesions With PSS/All Lesions (Prevalence of PSS)</th>
<th>Absent:Lesions With PSS/All Lesions (Prevalence of PSS)</th>
<th>( P )</th>
<th>Multivariable OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTO lesion</td>
<td>20/372 (5.4)</td>
<td>38/2709 (1.4)</td>
<td>&lt;0.0001</td>
<td>3.77 (1.98 to 7.17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LCX lesion</td>
<td>5/643 (0.8)</td>
<td>53/2438 (2.2)</td>
<td>0.02</td>
<td>0.21 (0.05 to 0.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>In-stent restenosis lesion</td>
<td>2/491 (0.4)</td>
<td>56/2590 (2.2)</td>
<td>0.006</td>
<td>0.23 (0.06 to 0.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>Lesion length &gt;17 mm</td>
<td>24/1852 (3.7)</td>
<td>14/1229 (1.1)</td>
<td>0.01</td>
<td>1.65 (0.91 to 3.00)</td>
<td>0.1</td>
</tr>
<tr>
<td>RCA lesion</td>
<td>30/1185 (2.5)</td>
<td>28/1896 (1.5)</td>
<td>0.04</td>
<td>1.29 (0.69 to 2.39)</td>
<td>0.42</td>
</tr>
<tr>
<td>Reference diameter &gt;2.83 mm</td>
<td>37/1529 (2.4)</td>
<td>21/1552 (1.4)</td>
<td>0.05</td>
<td>1.13 (0.63 to 2.03)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

PSS indicates peri-stent contrast staining; OR, odds ratio; CI, confidence interval; CTO, chronic total occlusion; LCX, left circumflex coronary artery; and RCA, right coronary artery.
to occur more frequently in the PSS group than in the non-PSS group (Figure 4).

The duration of follow-up in the long-term follow-up population after the first follow-up angiography was significantly longer in the PSS group (median 1113 [Q1 to Q3: 819 to 1407] days) than in the non-PSS group (median 896 [Q1 to Q3: 627 to 1239] days; P<0.0001). Subsequent TLR procedures were performed in 8 lesions with PSS and in 146 lesions without PSS. Cumulative incidence of subsequent TLR in the PSS group was numerically higher than that in the non-PSS group (15.0% versus 6.5% at 3 years; Figure 5). Subsequent ST occurred in 3 lesions with PSS and in 7
lesions without PSS. Cumulative incidence of subsequent definite ST in the PSS group also was numerically higher than that in the non-PSS group (8.2% versus 0.2% at 3 years; Figure 6). All 3 cases with ST in the PSS group were classified as VLST, and 2 lesions out of these 3 lesions had revealed progressive increase in the severity of PSS over time before the onset of VLST (Table 5). A representative case of VLST with progressive PSS is illustrated in Figure 3B.

Because we found significant association of PSS with stent fracture, we evaluated the influence of stent fracture on subsequent TLR in the PSS group as well as in the non-PSS group. The incidence of subsequent TLR was not different regardless of the presence or absence of stent fracture in the PSS group (Figure 7A). In the non-PSS group, the incidence of subsequent TLR appeared to be higher in lesions with stent fracture than in lesions without stent fracture (Figure 7B). Cumulative incidence of all-cause death was 10.7% in the PSS group and 6.3% in the non-PSS group, respectively, at 3 years after index follow-up angiography.

Discussion

The primary findings of this study are as follows: (1) Abnormal angiographic findings named PSS were found in 1.9% of lesions or 2.5% of patients within 12 months after SES implantation; (2) inter- and intra-observer variability analysis for diagnosis of PSS showed an almost perfect degree of agreement; (3) the independent risk factor for PSS was CTO whereas negative risk factors for PSS were left circumflex coronary artery lesion and in-stent restenosis lesion; and (4) lesions with PSS within 12 months after SES implantation were associated with higher rates of subsequent TLR as well as VLST compared with lesions without PSS.

In the current report, we propose a new definition and classification of abnormal angiographic findings after DES implantation, termed PSS, including those that do not fulfill the classic definition of CAA. Because this type of contrast staining outside the stent struts classified as PSS very rarely had been seen after bare-metal stent implantation, PSS could be regarded as representing an abnormal vessel wall response.

Table 5. Clinical Characteristics of Patients With PSS and Subsequent VLST

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age, y</th>
<th>Sex</th>
<th>DM, Yes/No</th>
<th>Morphology of PSS</th>
<th>Time From PCI to First FUCAG, d</th>
<th>Time From PCI to Second FUCAG, d</th>
<th>Progression of PSS</th>
<th>Time From PCI to VLST, d</th>
<th>Time From Diagnosis of PSS to VLST, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>Male</td>
<td>No</td>
<td>Segmental smooth</td>
<td>112</td>
<td>Not done</td>
<td>Not evaluated</td>
<td>471</td>
<td>359</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>Male</td>
<td>Yes</td>
<td>Segmental smooth</td>
<td>246</td>
<td>612</td>
<td>Yes</td>
<td>1083</td>
<td>839</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>Female</td>
<td>No</td>
<td>Segmental irregular</td>
<td>93</td>
<td>252</td>
<td>Yes</td>
<td>1114</td>
<td>1021</td>
</tr>
</tbody>
</table>

PSS indicates peri-stent contrast staining; DM, diabetes mellitus; PCI, percutaneous coronary intervention; FUCAG, follow-up coronary angiography; and VLST, very late stent thrombosis.
to DES. Coronary artery aneurysm and a mild form of PSS could be regarded as a continuum of vessel wall pathological process at the site of DES implantation. The observed prevalence of PSS (1.9% per lesion and 2.5% per patient) was lower than the reported prevalence of ISA by IVUS (5% to 13%) reflecting a higher sensitivity of IVUS in detecting ISA. \[10–12\] Therefore, PSS could be regarded as a relatively severe form of ISA.

Although the mechanisms of VLST after DES implantation are currently poorly understood, association between late acquired ISA and VLST has been suggested by several IVUS studies demonstrating very high prevalence (73% to 77%) of ISA with positive remodeling of the vessel wall in the setting of VLST. \[13–15\] Cook et al evaluated 10 patients with VLST by both IVUS and histological examination of aspirated thrombi, demonstrating that VLST was associated with histopathological signs of inflammation and IVUS evidence of positive vessel remodeling. \[14\] They also demonstrated that eosinophilic infiltrates were more common in thrombi harvested from patients with VLST compared with other causes of myocardial infarction suggesting the presence of chronic inflammation and/or hypersensitivity in these DES-treated lesions with ISA and positive remodeling. Histopathological investigations in human autopsy specimens of VLST are currently very limited. However, Virmani et al performed postmortem evaluation of a patient suffering from VLST after SES implantation. \[7\] Histopathological analysis revealed extensive inflammation in the intima, media, and adventitia consisting predominantly of lymphocytes and eosinophils associated with aneurismal dilatation of the vessel wall, malapposition of the stent struts, and thick fibrin thrombus between the stent struts and the arterial wall. More recently, Kon et al reported a case with VLST of SES demonstrating serial changes in PSS leading to aneurysm formation, as well as histopathological evidence of hypersensitivity vasculitis in the stented segment. \[22\] Therefore, accumulating evidence suggests that VLST associated with ISA and/or PSS might be mechanistically related to chronic inflammatory reactions. Inflammation leading to destruction of the medial wall might lead to loss of elastic vessel integrity and aneurismal dilatation.

In this study, patients with PSS in whom multiple lesions were treated with SES were prone to have PSS in multiple lesions, suggesting involvement of some patient-related factors in the formation of PSS. However, clinical characteristics predisposing to PSS formation were not clearly identified in this study because of the small number of lesions with PSS. The prevalence of stent fracture in lesions with PSS was markedly higher than that in lesions without PSS. Doi et al reported that 5 lesions (all treated with SES) out of 20 consecutive lesions with evidence of stent fracture by IVUS were associated with coronary aneurysm. \[23\] It was postulated that biological reactions to the DES cause positive remodeling with aneurysm formation and malapposition; aneurysm formation and malapposition may allow motion and/or kinking of the stent within the aneurysm, leading to stent fracture.

In the current analysis, the incidences of early and late TLR tended to be higher in lesions with PSS than in lesions without PSS, suggesting that possible inflammatory reactions underlying PSS formation might be involved in the restenosis process of SES. Also, cumulative incidence of VLST in lesions with PSS was numerically higher than that in lesions

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**Figure 7.** Influence of stent fracture on cumulative incidence of TLR after the index follow-up angiography in the PSS group (A) and in the non-PSS group (B). PSS indicates peri-stent contrast staining; SF, stent fracture.
without diagnosis of PSS. Therefore, it would be reasonable to regard patients with PSS as being at high risk for subsequent VLST. These observations might suggest that common mechanisms such as chronic inflammation might be operative for both VLST and restenosis requiring TLR.

Our current findings suggest that morphological changes seen within 12 months after SES implantation might impact long-term clinical outcome. If PSS could be proven to be a very strong correlate of late adverse outcome in a larger number of patients, we should look for optimal management of patients with PSS. However, optimal management of patients with a diagnosis of PSS is currently unknown. Intuitively, dual antiplatelet therapy should be continued indefinitely in patients with PSS. It has not yet been clarified whether the culprit for thrombosis in lesions with PSS is the separation of stent struts from the vessel wall itself or inflammatory responses underlying the separation of stent struts from the vessel wall. Therefore, an aggressive effort to maximize apposition of stent struts to the vessel wall might not be recommended. Furthermore, it is currently uncertain whether every patient who has received SES should undergo control angiography at 8 months. However, given the markedly increased risk for VLST, very close clinical follow-up should be mandatory when PSS is found during follow-up after DES implantation.

Study Limitations
There are several important limitations in this study. First, the number of patients with PSS was relatively small to investigate the risk factors of PSS and to evaluate a possible correlation between morphological classification and risk of VLST. Also, risk stratification for VLST according to the status of antiplatelet therapy could not be conducted because of the small number of patients with PSS. Second, although we found apparent association between PSS and stent fracture, we could not address which of the 2 angiographic findings was the stronger correlate of a late adverse event. Third and most importantly, the number of patients with VLST after diagnosis of PSS was very small, rendering the estimation of the incidences of VLST relatively inaccurate. The real incidences and risk factors of VLST and TLR after PSS diagnosis should be evaluated in a larger number of patients with longer follow-up duration.

Conclusions
Abnormal angiographic findings named PSS were found in 1.9% of lesions (2.5% of patients) within 12 months after SES implantation. Peri-stent constrast staining found within 12 months after SES implantation seemed to be associated with subsequent TLR as well as VLST.

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Disclosures
Dr Kimura has served as an advisory board member for Cordis Cardiology, Abbott Vascular, and Terumo. Dr Kouzuma has served as an advisory board member for Abbott Vascular, Terumo, and Nipro. Dr Kadota has served as an advisory board member for Abbott Vascular. The remaining authors report no conflicts.

References
We have noted abnormal angiographic findings at the site of drug-eluting stent implantation, suggesting contrast staining outside the stent struts that do not fulfill the classic definition of coronary aneurysm. We propose a new term, peri-stent contrast staining (PSS), for these abnormal angiographic findings and assess their incidence, risk factors, and clinical sequelae. Peri-stent contrast staining was defined as contrast staining outside the stent contour, extending to ≥20% of the stent diameter. The study population consisted of 3081 lesions (1998 patients) that were treated exclusively with sirolimus-eluting stents and were evaluated by follow-up angiography within 12 months after sirolimus-eluting stent implantation. Late acquired PSS was observed in 58 lesions (1.9%) in 49 patients (2.5%). The independent risk factor of PSS was chronic total occlusion, whereas negative risk factors for PSS were left circumflex coronary artery lesion and in-stent restenosis lesion. Stent fracture was more frequently observed in lesions with PSS than in lesions without PSS (43.1% versus 5.4%, \( P < 0.0001 \)). Cumulative incidence of target-lesion revascularization and definite very late stent thrombosis at 3 years after the index follow-up angiography in the PSS group was higher than that in the non-PSS group (15.0% versus 6.5%, and 8.2% versus 0.2%, respectively). Peri-stent contrast staining found within 12 months after sirolimus-eluting stent implantation appeared to be associated with subsequent target-lesion revascularization and very late stent thrombosis. Although the real incidences and risk factors of very late stent thrombosis and target-lesion revascularization after PSS diagnosis should be evaluated in a larger number of patients with longer follow-up duration, patients with PSS should be followed up very carefully.
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