Healing course of acute vessel wall injury after drug-eluting stent implantation assessed by optical coherence tomography

Dries De Cock1*, Johan Bennett1, Giovanni J. Ughi2, Christophe Dubois1,2, Peter Sinnaeve1,2, Jan Dhooge2, Walter Desmet1,2, Ann Belmans3, and Tom Adriaenssens1,2

1Department of Cardiovascular Diseases, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Leuven, Belgium; 2Department of Cardiovascular Sciences, Katholieke Universiteit Leuven, Leuven, Belgium; and 3Interuniversity Institute for Biostatistics and Statistical Bioinformatics, Katholieke Universiteit Leuven, Leuven, Belgium

Received 9 November 2013; accepted after revision 2 January 2014; online publish-ahead-of-print 4 February 2014

Background

Vessel wall injury after drug-eluting stent (DES) implantation can be characterized in detail by optical coherence tomography (OCT). Little is known about the healing course of these phenomena.

Methods and results

In 62 lesions (62 patients), the incidence of acute vessel trauma was assessed in the stented region and the edge segments immediately after DES implantation. The healing course of these injuries was assessed at 9-month OCT follow-up using a software algorithm allowing for reliable spatial comparison of baseline and follow-up cross-sectional images. Tissue prolapse (TP) and tissue protrusions were detected in 81 and 35% of lesions, respectively. A total of 342 intra-stent dissection flaps (ISD) and 114 intra-stent dissection cavities (ISC) were visualized in 98 and 81% of lesions, respectively. Thirty-five lesions (56%) showed edgedissections (EDs). No residual TP or protrusion was observed at follow-up. Incomplete healing was seen in 8% of ISD and in 20% of ISC. For ED, a residual flap was observed in one-third of the initially dissected stent edges. Incomplete healing of acute vessel injury was associated with the presence of underlying atherosclerotic disease at baseline. Uncovered and malapposed stent struts were observed more often with incomplete healing of vessel injury at follow-up.

Conclusions

Acute vessel wall trauma is highly prevalent immediately after DES implantation. Most of these injuries are minor and resolve at mid-term follow-up. Incomplete healing of ISDs seems to be associated with other OCT findings suggesting delayed arterial healing.

Keywords

edge dissection • intra-stent dissection • tissue prolapse • optical coherence tomography • drug-eluting stent

Introduction

Percutaneous coronary intervention (PCI) with stent implantation is inherently associated with a certain degree of injury to the vessel wall. Assessment with optical coherence tomography (OCT) in some recent studies has revealed that this vessel wall injury occurs more frequently than previously expected.1,2 Different types of vessel damage [tissue prolapse (TP), intra-stent dissection flaps (ISD), intra-stent dissection cavities (ISC), and edge dissection (ED)] can be visualized in detail with OCT, even when they are not detectable by angiography or intravascular ultrasound (IVUS), the former gold standard in intracoronary imaging.2–6

Given the high incidence of these findings following PCI and their possible link with future adverse clinical events such as stent thrombosis (ST) and in-stent restenosis (ISR), a clear insight into the natural healing course of these phenomena is important.7,8 The unsurpassed spatial resolution of OCT (< 20 μm) offers unique opportunities for the in vivo assessment of the healing course of vessel damage after stent implantation. However, until present, corresponding frames in serially acquired OCT pullbacks could only be compared manually, based on specific anatomical landmarks, such as side branches or calcified plaques.9 Using a dedicated software algorithm, specifically developed and validated at our institution for this purpose, we are able to perform frame-by-frame comparative analyses of OCT images acquired at different time points.10

The objectives of our study were as follows: (i) to describe the incidence of ISD, ISC, and ED, as well as the incidence of TP, tissue protrusion, and residual red thrombus immediately after drug-eluting...
stent (DES) implantation and (ii) to assess the healing course of these phenomena at 9-month follow-up, comparing sequential OCT pullbacks using this dedicated software algorithm.

**Methods**

**Study population**

Pullbacks from all patients undergoing OCT immediately and 9 months after DES implantation in a single-centre, randomized clinical trial (STAC-CATO, NCT 1065519) were used for this analysis. In this trial, patients were stratified according to their presentation with ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) or stable/unstable angina (SAP/UAP) and randomized to treatment with everolimus-eluting stents with a durable polymer (EES: Xience V/PrimeTM, Abott Vascular, Santa Clara, CA, USA) or bioelims A9-eluting stents with a biodegradable polymer (BES: BiomatrixTM, Biosensors International, Morges, Switzerland). Although multivessel PCI was allowed, only one predefined lesion per patient was considered for OCT imaging.

**Quantitative coronary angiographic evaluation**

Digital coronary angiograms were analysed offline using a validated automated edge dissection system (APCOM.PC 5.0, Siemens, Germany). Minimum lumen diameter (MLD), reference vessel diameter (RVD), and lesion length were evaluated before PCI.

**OCT acquisition**

OCT was performed using the FD-OCT system (C7-XR Intravascular Imaging System and Dragon Fly OCT catheter, St. Jude Medical, St. Paul, MN, USA) with a pullback speed of 20 mm/s and a frame rate of 100 frames/s, using a non-occlusive flushing technique. Intracoronary nitroglycerine (100–300 µg) was given before starting the intracoronary imaging procedure. An automated pullback was started ≥ 5 mm distally from the most distal stent struts as soon as the lumen was cleared from blood using an automated flush of contrast dye.

**OCT analysis**

All baseline OCT images were reviewed by an independent observer who was blinded to the clinical presentation and the lesion and procedural characteristics. The region analysed comprised the stented segment and the edge segments (i.e. the vessel segments 5 mm proximal and distal to the stented segment). Cross-sectional OCT images were analysed at every frame (0.2-mm intervals) with the use of an offline workstation with integrated image analysis software (St. Jude Medical) for the presence of ISD, ISC, TP, ED, tissue protrusion, and red thrombus.

ISD was defined as a disruption of the luminal vessel surface in the stent segment with a dissection flap protruding in the lumen. When a dissection flap was visualized, the maximum length of the flap (from its tip to the joint point with the vessel wall) was measured in the cross-sectional images. Only dissection flaps extending ≥ 200 µm into the lumen were considered (Figure 1A).

ISC was defined as a disruption of the luminal vessel surface in the stented segment with an underlying cavity in the vessel wall. The maximum depth of the cavity (from the lumen to the deepest point

---

**Figure 1** Representative OCT images of acute vessel wall injury immediately after DES implantation showing ISD (A), ISC (B), TP (C), ED (D), and tissue protrusion (E,F). For ED and ISD, the maximal flap length was measured (magnified image in panels A and D); for ISC, the maximal cavity depth was measured (magnified image in panel B); and for TP, the maximal protrusion length and area in the lumen were measured (magnified image in panel C). Tissue protrusion was defined as an irregular structure attached to the vessel wall (E) or the stent struts (F) and protruding beyond the struts into the lumen. Note the malapposed struts at the site of tissue protrusion in panel F (white arrows).
inside the vessel wall) was measured in the cross-sectional images. Only dissection cavities with a depth of \( \geq 200 \) \( \mu m \) were considered (Figure 1B).

TP was defined as convex-shaped tissue with a regular surface protruding between adjacent stent struts towards the lumen, without disruption of the continuity of the luminal vessel surface.\(^5\) The maximal prolapse of tissue was measured and was defined as the distance from the arc connecting adjacent stent struts to the greatest extent of prolapse into the lumen (TP length). Only TP sites with tissue protruding \( \geq 200 \) \( \mu m \) in the lumen were considered. The maximum area of tissue protruding adjacent stent struts was also measured (TP area) (Figure 1C).

The number of sites of TP, ISD, or ISC per stent was counted, as was the number of frames per site in which the phenomenon was observed. To take into account differences in stent length, the number of frames with TP, ISD, or ISC was normalized for the total number of frames per stent segment.

ED was defined as a disruption of the vessel luminal surface within 5 mm proximal and distal to the stent with the presence of a visible flap. Maximum flap length (from its tip to the joint point with the vessel wall) was measured in the cross-sectional images; the longitudinal extension of the dissection along the vessel wall was determined by the number of cross-sectional images with visible dissection, multiplied by 0.2 mm (Figure 1D).

The plaque type at the stent edges and at the site of TP, ISC, and ISC was assessed by OCT. We classified the plaque types as follows: (i) fibrous (homogeneous signal rich), (ii) fibrocalcific (signal poor with defined borders), (iii) lipid-rich (signal poor with diffuse borders), or (iv) mixed (lipid-rich/calcified).\(^12\) If the vessel wall exhibited the normal three-layered structure or mild intimal thickening (intima thickness \( \leq 250 \) \( \mu m \)), it was considered free of atherosclerotic plaque.

Tissue protrusion was defined as a mass with an irregular surface attached to the vessel wall or to the stent struts and protruding beyond the struts into the lumen.\(^13\) Red thrombus was defined as an intraluminal mass discontinuing of the surface of the vessel wall with a signal-free shadow behind the structure.\(^14\) The underlying plaque type was not determined for tissue protrusions and red thrombi, because in most cases a high degree of attenuation behind the protruding mass precluded proper evaluation (Figure 1E and F).

The healing of acute vessel injury was assessed using a previously described software algorithm for spatial registration of OCT datasets acquired at different time points in the same patient. The algorithm was developed at our institution, and its concept and validation were described earlier.\(^10,15,16\) In brief, stent struts are segmented through consecutive images and three-dimensional models of the stents are created for both datasets to be registered. There is a first relatively rough registration of the two models through an automatic initialization procedure, and an iterative closest point algorithm is subsequently applied for a more precise registration. To correct for non-uniform rotational distortion and other potential acquisition artefacts, the registration is refined at a local level. The images are then presented in a graphical user interface,
Late malapposition was defined as separation of one or more stent struts from the vessel wall, in a vessel segment not encompassing a side-branch origin. A stent strut was considered malapposed when the distance between the centre reflection of the strut and the vessel wall was greater than the thickness of the stent strut. The threshold for malapposition distance was calculated as the strut thickness + the polymer coating of the stent + half of the blooming artefact (18 mm). This resulted in a threshold of ≥110 μm for EES and 150 μm for BES. Uncovered stent struts were defined as struts without a visible tissue layer on the centre reflection of the strut. Intersut cavities were suspected when the luminal vessel contour extended in a pouch-like fashion beyond the line connecting the struts (sten contour). The stent contour in the image was traced manually, and the distance between the stent contour and the bottom of the cavity was measured. When the maximal distance exceeded 250 μm, we considered the outward bulging as an IC.

Finally, mean lumen area, mean stent area, and mean neointimal area were quantified automatically for the follow-up OCT pullback, as previously described.
In a subset of patients with OCT pullbacks acquired before stent implantation, the images at the site of minimal lumen area (‘culprit site’) in the lesion were analysed with validated criteria for plaque characterization as reported previously. Thin-cap fibroatheroma (TCFA) was defined as a lipid pool with a thin overlying fibrous cap measuring ≤80 µm at the thinnest part. Thrombus at the culprit site was identified as an intraluminal mass discontinuing from the surface of the vessel wall. Red thrombi were defined as intraluminal projections with a signal-free shadow.

**Clinical follow-up**

The incidence of death, non-fatal myocardial infarction, ST, and target lesion revascularization (TLR) was evaluated at 9 months. TLR was defined as any intervention (surgical or percutaneous) of the analysed lesion.

**Statistical analysis**

Statistical analyses were performed using SAS software version 9.2. Continuous variables are presented as means and SD. For variables that showed clear deviations from a normal distribution, medians and inter-quartile ranges (IQR) are reported. Categorical variables are presented using frequency counts and percentages. Univariate associations between incomplete healing of ED, ISC, and ISD and baseline variables, as well as the association between incomplete healing of ISC and ISD and the presence of late malapposition, uncovered struts, and IC, were assessed using GEE models for logistic regression with an unstructured variance–covariance matrix to account for possible correlations within patients. All tests were two-sided and assessed at a significance level of 5%. Owing to the exploratory nature of the study, no adjustment was made to the significance level to account for multiple testing.

**Results**

**Study population**

Sixty-four patients (64 vessels) underwent OCT imaging immediately after stent implantation. Two lesions were excluded because of insufficient image quality of the initial OCT pullback. Of the 62 lesions evaluated with OCT at baseline, 12 were excluded for the comparative analysis: 7 patients did not consent with a follow-up angiography and OCT imaging procedure, 1 patient experienced early vessel closure for which an additional DES was implanted, in 2 patients the image quality of the follow-up OCT images was insufficient for analysis, and in another 2 patients more than 1 OCT pullback was required to visualize the entire stented segment, making a frame-by-frame analysis with the software algorithm impossible. In the remaining 50 lesions, a comparative analysis of serial OCT images was performed.

**Patient and procedural characteristics**

Baseline patient demographic, lesion, and procedural characteristics are shown in Table 1. There were no major complications during the OCT examinations, apart from one patient, treated for STEMI, who suffered distal embolization of thrombus during the OCT examination, which resolved after balloon dilation at low pressure distally in the target vessel.

**OCT findings**

Qualitative and quantitative assessment of the different types of acute vessel injury is shown in Table 2. Tissue protrusions were seen at 43 sites in 22 lesions (35%) and were more frequently observed in patients presenting with STEMI (57%) compared with patients with NSTEMI (37%) and UAP/SAP (14%, P = 0.01). Tissue protrusions containing red thrombus were visible at 20 sites in 14 lesions (23%). OCT imaging before stent implantation was performed in 49 of 62 patients. Table 3 shows the assessment of plaque morphology at the culprit site on pre-intervention OCT. ISC was seen more often when a >180° calcified plaques was present (P = 0.02); tissue protrusion...
was more frequent when TCFA or thrombus was detected ($P = 0.006$ and $< 0.001$, respectively).

Out of 342 ISDs detected after stenting, 74 could not be assessed at follow-up. Of the remaining 268 ISDs, 8% showed a residual flap. For the 114 ISCs identified at baseline, 26 could not be assessed at follow-up. Of the remaining 88 ISCs, 20% were incompletely healed at follow-up. We were able to assess the healing in 110 of 125 TP sites and in 41 of 43 sites of tissue protrusion. No residual TP or protrusion was observed in the follow-up OCT images. For ED, healing status of the dissection flaps was assessed in 20 of 23 distal EDs and 11 of 17 proximal EDs. A residual flap was observed at the distal edge in 30% and at the proximal edge in 27% of the initially dissected stent edges. Representative OCT images demonstrating incompletely healed and resolved vessel wall injury at 9-month follow-up are shown in Figure 3.

Incomplete healing at 9 months was related to the extent of vessel injury at baseline for ISC. A similar trend was observed for ED and ISD (Table 4). ISD/ISC was less likely to be resolved when the underlying

Figure 3 Representative OCT images: (A) incomplete healing at 9-month follow-up of ED (i), ISD (ii), and ISC (iii); (B) completely healed ED (i), ISD (ii), and ISC (iii); (C) multiple IC (asterisks).
vessel wall showed atherosclerotic disease. This was observed in particular when the underlying plaque type was mixed. No significant association between incomplete healing of vessel injury and plaque morphology on pre-intervention OCT was found. A trend towards more residual dissection was seen in lesions with >180° calcified plaques at the culprit site. On the other hand, there was a trend towards better healing of vessel injury when thrombi were present before stent implantation (Table 5). Patients presenting with STEMI were less likely to have residual dissection at the stent edge at follow-up. There was a similar trend for better healing of ISD/ISC in STEMI patients, compared with patients presenting with NSTEMI or SAP/UAP. A non-significant association between the use of BES and incomplete healing of ISD/ISC at follow-up was observed. A similar trend was seen for the association between BES and residual dissection at the stent edge at follow-up (Table 5 and 6).

OCT findings suggesting delayed arterial healing were frequently observed at 9-month follow-up. Uncovered struts were seen in 6 and 11% at the site of initial ISD and ISC, respectively. Malapposed struts were observed in 3% of sites of initial ISD and 2% of sites of initial ISC. The incidence of IC was 13 and 20% for ISD and ISC, respectively. No late malapposition was observed at follow-up at sites of initial TP. Uncovered struts and IC were observed in 4 and 13% of initial TP sites, respectively. For tissue protrusion, no late malapposition or IC were observed at follow-up; uncovered struts were seen in 5% of initial sites of tissue protrusion. Incomplete healing of ISD and ISC was observed in association with delayed arterial healing, as detected by OCT. In the follow-up OCT images, uncovered struts [18 vs. 7%, OR = 2.9 (1.2–7.1), P = 0.01] and IC [33 vs. 13%, OR 3.4 (1.2–9.4), P = 0.02] were more frequently observed when a residual flap or cavity was present. Even so, late strut malapposition [8 vs. 2%, OR 4.3 (0.87–21.4), P = 0.07] was seen more often with incompletely healed intra-stent injury, although the association was not significant (Figure 4). Furthermore, mean area of neointimal hyperplasia and percentage mean area of neointimal hyperplasia were significantly smaller in lesions with incompletely healed injury, compared with lesions with resolved vessel wall trauma (Table 7).

**Clinical outcome**

There were no deaths at 9-month follow-up. One patient suffered acute vessel closure owing to distal ED immediately following the procedure and was treated with implantation of an additional DES.

---

**Table 4** Association between incomplete healing of ED, ISD, and ISC and the 'initial size' of the acute vessel wall effect

<table>
<thead>
<tr>
<th>Initial size of the effect</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>Length of dissection flap (increase of 10 μm)</td>
<td>1.028 (0.997–1.060)</td>
</tr>
<tr>
<td>ISD</td>
<td>Length of dissection flap (increase of 10 μm)</td>
<td>1.013 (0.999–1.026)</td>
</tr>
<tr>
<td>ISC</td>
<td>Depth of dissection cavity (increase of 10 μm)</td>
<td>1.035 (1.005–1.065)</td>
</tr>
</tbody>
</table>

ED, edge dissection; ISD, intra-stent dissection; ISC, intra-stent cavity.

**Table 5** Association between incomplete healing of 'intra-stent dissection and intra-stent cavity' and baseline clinical, procedural, and lesion variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of DES</td>
<td>BES/EES</td>
<td>1.95 (0.85–4.47)</td>
</tr>
<tr>
<td>Plaque type</td>
<td>None/mixed</td>
<td>0.08 (0.008–0.79)</td>
</tr>
<tr>
<td></td>
<td>Fibrous/mixed</td>
<td>0.28 (0.091–0.83)</td>
</tr>
<tr>
<td></td>
<td>Calcified/mixed</td>
<td>0.44 (0.097–2.04)</td>
</tr>
<tr>
<td></td>
<td>Lipid/mixed</td>
<td>0.21 (0.068–0.63)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>Male/female</td>
<td>1.00 (0.96–1.04)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>1.36 (0.50–3.69)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>1.23 (0.56–2.69)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td></td>
<td>0.68 (0.24–1.96)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td></td>
<td>2.23 (0.94–5.30)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>STEMI vs. SAP/UAP</td>
<td>0.28 (0.09–0.84)</td>
</tr>
<tr>
<td></td>
<td>NSTEMI vs. SAP/UAP</td>
<td>0.70 (0.29–1.69)</td>
</tr>
<tr>
<td>Lipid pool &gt; 180°</td>
<td></td>
<td>0.79 (0.35–1.81)</td>
</tr>
<tr>
<td>Calculations &gt; 180°</td>
<td></td>
<td>1.62 (0.70–3.75)</td>
</tr>
<tr>
<td>TCFA present</td>
<td></td>
<td>0.92 (0.44–1.95)</td>
</tr>
<tr>
<td>Thrombus</td>
<td></td>
<td>0.66 (0.31–1.39)</td>
</tr>
</tbody>
</table>

*Estimated odds ratios and P-values were obtained using a GEE model with an unstructured variance–covariance matrix.
*Based on the assessment of plaque characteristics and the presence of thrombi at the site of minimal lumen area on pre-intervention OCT imaging (n = 49).

DES, drug-eluting stent; BES, biolimus-eluting stent; EES, everolimus-eluting stent; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; SAP, stable angina pectoris; UAP, unstable angina pectoris.
Apart from this patient, there were no TLR or any other major adverse cardiac event reported at 9-month follow-up.

**Discussion**

This study describes the natural healing course of acute vessel wall injury at mid-term follow-up using dedicated software for detailed frame-by-frame comparison of sequential OCT images. The main findings are as follows: (i) injury to the vessel wall is highly prevalent immediately after stent implantation, (ii) most of these injuries heal at mid-term follow-up, (iii) incomplete healing of ISD and ISC is associated with other OCT findings suggesting delayed arterial healing in DES, such as uncovered struts, late malapposition, and IC, (iv) these findings were, however, not associated with adverse clinical events at mid-term follow-up.

The incidence and the different types of acute vessel injury in our study cohort are in keeping with previous OCT studies.\(^1,2,5,9,24,25\) Until now, the long-term impact of vessel wall trauma in the stented segment has not been elucidated. Pathological studies have associated ST with the disruption of vessel continuity.\(^7\) Furthermore, an association between vessel injury and restenosis has been reported in animal and pathological studies.\(^8,26\) The current study is the first to report the healing characteristics of these vessel wall injury in detail using serial OCT imaging.

In the follow-up examinations of our dataset, TP was no longer visible in any of the pullbacks. Hence, TP, detected by OCT, appears to be a benign phenomenon. In previous IVUS studies, minor plaque prolapse was not associated with late angiographic ISR.\(^27,28\) Whereas TP is characterized by a smooth luminal surface, tissue protrusions present as irregular structures attached to the vessel wall or the stent struts and are therefore suggestive of thrombus with or without protrusion of plaque tissue components such as lipid content. Markedly, all of these intraluminal masses had disappeared at the time of follow-up. This observation suggests that these abnormalities correspond predominantly to intraluminal thrombus, which are compressed by stent inflation, subsequently protrude between the stent struts, and gradually resolve as a consequence of endogenous fibrinolysis and anticoagulant and antiplatelet therapy.

Residual dissection was observed in 8% of ISD, as compared with 21% of ISC. More extensive vessel damage at baseline and the presence of a mixed atherosclerotic plaque were predictors of residual dissection at follow-up. Probably, ISC extend deeper into the

---

**Table 6** Association between incomplete healing of ‘edge dissections’ and baseline clinical, lesional, and procedural variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of DES</td>
<td>BES/EES</td>
<td>5.05 (0.88–28.6)</td>
</tr>
<tr>
<td>Plaque type</td>
<td>None/mixed</td>
<td>1.67 (0.08–34.7)</td>
</tr>
<tr>
<td></td>
<td>Fibrous/mixed</td>
<td>3.33 (0.26–43.5)</td>
</tr>
<tr>
<td></td>
<td>Calcified/mixed</td>
<td>2.50 (0.10–62.6)</td>
</tr>
<tr>
<td></td>
<td>Lipid/mixed</td>
<td>1.67 (0.10–27.9)</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td>1.04 (0.96–1.14)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male/female</td>
<td>0.29 (0.06–1.39)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>1.70 (0.42–6.85)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>2.42 (0.40–14.5)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td></td>
<td>1.03 (0.16–6.49)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td></td>
<td>1.81 (0.21–15.9)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>STEMI vs. SAP/UAP</td>
<td>0.04 (0.005–0.34)</td>
</tr>
<tr>
<td></td>
<td>NSTEMI vs. SAP/UAP</td>
<td>0.68 (0.15–3.05)</td>
</tr>
</tbody>
</table>

*Estimated odds ratios and P-values were obtained using a GEE model with an unstructured variance–covariance matrix.

DEs, drug-eluting stent; BES, biolimus-eluting stent; EES, everolimus-eluting stent; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; SAP, stable angina pectoris; UAP, unstable angina pectoris.
vessel wall than ISD, corresponding to more extensive vessel wall damage baseline, making incomplete healing at follow-up more frequent. Several pathologic and OCT studies implicated plaque morphology at the culprit site as an important factor in delayed vessel healing after DES implantation. The structure of atherosclerotic plaques may affect arterial responses to stent placement through different mechanisms. Lipid-rich plaques are more avascular and have fewer smooth muscle cells compared with fibrous plaques. Therefore, these lesions are less likely to be covered by migrating cells from adjacent areas. Furthermore, the drug loaded on the stent is, in general, highly lipophilic. It is likely that these agents have greater affinity for lipid-rich and mixed plaques, giving rise to higher drug concentration and a more sustained release, hence retarding smooth muscle cell proliferation and endothelial regrowth.

Residual dissection flaps or cavities were associated with late malapposition, uncovered struts, and IC, which are associated with late adverse outcome after DES implantation. Since the observational nature of our study, the association between incomplete healing of ISD and ISC on the one hand and late malapposition and IC on the other hand can only be considered as hypothesis-generating. A recent OCT study related protruding and malapposed struts at follow-up to angiographic dissection at baseline. Positive vessel remodelling, secondary to inflammation caused by deeper penetration of the drug into the vessel wall as a consequence of intimal disruption, was suggested as a possible explanation for this finding. An alternative explanation is that incomplete healing of intra-stent vessel injury is just another manifestation of delayed arterial healing after DES implantation. Lesions with incompletely healed vessel injury showed a lower degree of neointimal hyperplasia in our study. Furthermore, a higher incidence of incomplete healing in BES- vs. EES-treated lesions was observed. In the primary analysis of the STACCATO study, a better suppression of neointimal growth, reflected by a higher incidence of uncovered struts and a lower mean neointimal thickness, was observed in lesions treated with BES as compared with lesions treated with EES.

Data on the impact of EDs on acute and long-term outcome after PCI are conflicting. Although data about the healing course of EDs are scarce, previous studies reported complete healing of stent EDs at 6- to 8-month follow-up. In our study population, residual dissection flaps were observed in a quarter of the dissected edges at mid-term follow-up. Whether these residual EDs heal further in the long term remains to be determined in sequential OCT studies with longer follow-up.

The absence of clinical events, despite a significant proportion of intra-stent and EDs with incomplete healing status at 9-month follow-up, shows that these phenomena are either benign or reflect a dynamic process with further resolution at long-term follow-up. Likewise, previous studies using serial OCT failed to demonstrate an association between inappropriate vessel wall healing and clinical events. These studies, like ours, included a relatively low number of patients and reflect a lower-risk population than in daily practice, precluding firm conclusions regarding clinical outcome.

Limitations

The lack of long-term follow-up OCT data to assess the natural healing course of the described vessel wall injury is the major limitation of this study. Follow-up OCT was performed at a 9-month interval, because this was predefined in the methodology of the STACCATO study. It cannot be excluded that these residual dissection flaps and/or cavities completely heal at longer-term follow-up. Secondly, our study was not sufficiently powered to assess the clinical relevance of OCT-assessed vessel injury and its healing course. Thirdly, a significant number of lesions evaluated with OCT after stent implantation could not be analysed at follow-up. Therefore, the healing status of ~20% of acute vessel wall effects could not be assessed. Fourthly, the association between residual dissection at follow-up and the underlying plaque type at baseline should be addressed with caution. Owing to distortion and compression of the atherosclerotic material and the interference of the blooming artefacts of the stent struts, evaluation of the morphologic characteristics of atherosclerotic plaques immediately after PCI can be challenging. Finally, some arbitrary cut-offs were used for the quantitative description of the different types of vessel injury baseline, excluding minor vessel wall trauma, for which we assumed spontaneous resolution and appropriate healing at follow-up.

Conclusion

Periprocedural vessel wall injury can be characterized in detail using OCT and is ubiquitously seen after DES implantation. Most of these abnormalities are minor and resolve spontaneously within 9 months. When the initial trauma is an ISC and when the underlying vessel wall shows mixed atherosclerotic plaque, incomplete healing at mid-term follow-up is seen more often. Incomplete healing of vessel injury seems to be associated with other signs of delayed arterial healing, i.e. uncovered and malapposed struts and IC.

Conflict of interest: none declared.

Table 7  Quantitative OCT analysis ‘at 9-month follow-up’ in stented lesions showing incomplete healing of vessel injury vs. lesions with only resolved vessel wall trauma

<table>
<thead>
<tr>
<th></th>
<th>Lesions with incompletely healed vessel injury (n = 26)</th>
<th>Lesions with resolved vessel injury (n = 24)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean lumen area (mm²)</td>
<td>7.2 ± 2.1</td>
<td>7.0 ± 2.4</td>
<td>0.851</td>
</tr>
<tr>
<td>Mean stent area (mm²)</td>
<td>7.4 ± 2.1</td>
<td>7.7 ± 2.4</td>
<td>0.638</td>
</tr>
<tr>
<td>Mean neointimal hyperplasia area (mm²)</td>
<td>0.6 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>0.022</td>
</tr>
<tr>
<td>Neointimal hyperplasia area (%)</td>
<td>8.3 ± 3.7</td>
<td>11.9 ± 8.3</td>
<td>0.047</td>
</tr>
</tbody>
</table>

D. De Cock et al.
References


