CLINICAL RESEARCH

Spatial distribution of neo-intimal hyperplasia 6 months after zotarolimus-eluting stent implantation, analysed by optical coherence tomography

Distribution spatiale de l’hyperplasie néo-intimale six mois après implantation de stents actifs au zotarolimus analysée par tomographie par cohérence optique

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Received 10 September 2010; received in revised form 9 December 2010; accepted 17 December 2010

Summary

Background. — Optical coherence tomography is a high-resolution imaging technology that allows in vivo assessment of neointimal hyperplasia and strut coverage after coronary stenting. Aim. — Assessment of spatial distribution of healing, 6 months after zotarolimus-eluting stent implantation. Methods. — Forty-two zotarolimus-eluting stents were monitored by optical coherence tomography 6 months after implantation. Mean neointimal strut coverage thickness and percentage of neointimal hyperplasia were measured every millimetre. Non-covered strut ratios were assessed on each slice. In addition, the spatial distribution of neo-intimal hyperplasia and strut coverage were analysed longitudinally on five stent segments and axially on each slice.

KEYWORDS

Optical coherence tomography; Neointimal hyperplasia; Zotarolimus-eluting stent

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Results. — There were no clinical events at 6 months under dual antiplatelet therapy. The optical coherence tomography analysis showed a mean neointimal hyperplasia thickness of 333 ± 147 μm and neointimal hyperplasia obstruction of 36.1 ± 12.3%. The percentage of covered struts at 6 months was very high (98.9%). Only 6/745 slices analysed (0.8%) had non-covered strut ratios exceeding 30%. There was no significant heterogeneity in either longitudinal or axial neointimal hyperplasia distribution. No thrombi were observed.

Conclusion. — This optical coherence tomography study found relatively constant neointimal hyperplasia thickness, regardless of the zotarolimus-eluting stent length or diameter. This spatially homogeneous neointimal hyperplasia was associated with near-total coverage of all struts, 6 months after implantation.

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Background

Randomised studies have shown that DESs significantly reduce clinical restenosis rates compared with bare-metal stents [1—4]. This benefit is due to inhibition of intimal neoproliferation [5]. Animal and autopsy studies, however, have shown this effect to be associated with delayed or deficient arterial healing. It is therefore advisable to continue dual antiplatelet therapy beyond the first month post stenting, in order to avoid late intrastent thrombosis [6]. In a series of 8000 DESs, Wenaweser et al. reported a consistent 0.6% annual late thrombosis rate over the first 4 years post stenting [7].

Intrastent thrombosis is a multifactorial phenomenon [8], but one significant factor is failure of stent–strut re-endothelialization [9]. Post-mortem studies of stented subjects [10] have reported deficient re-endothelialization to be more frequently associated with late intrastent thrombosis than with other causes of death [11,12].

OCT is a high-resolution (around 10 microns) imaging technology that is particularly well adapted for the study of the most superficial layers of the vessel wall and for strut-by-strut stent analysis. Several recent studies have focused on OCT analysis of neointimal coverage in bare-metal and first-generation DESs [13—16]. The present study used OCT to quantify and analyse the spatial distribution of NIH and strut coverage, 6 months after ZES implantation.

Methods

Study population and methods

Between October 2006 and September 2007, 25 patients (21 men, four women) gave consent and were included in this prospective, observational study. These 25 patients were selected from the 220 patients who underwent ZES implantation in our centre during the study period, using the following inclusion criteria: consent and feasibility of OCT. Exclusion criteria were left main coronary artery stenosis, bypass lesion, ostial stenosis, renal insufficiency, acute coronary syndrome, stent overlapping, contraindication for DES and OCT limitations. OCT limitations were tortuous and
Zotarolimus-eluting stent analysed by OCT

Optical coherence tomography procedure

Optical coherence tomography at 6 months post stenting immediately followed the control angiography. A 6F catheter was used to inject 30 UI/kg of unfractionated heparin intravenously. A 0.014-inch guide was introduced into the vessel and positioned distally to the stent. A Helios™ coaxial occlusion balloon catheter (LightLab Imaging, Westford, MA, USA) was then introduced along the guide across the vessel until the balloon marker was at the distal extremity of the stent. The guide was then withdrawn and replaced by a 1.4F optic fibre, connected up to the OCT system (M2 version, LightLab Imaging, Westford, MA, USA) and inserted through the balloon until distal to the stent. The occlusion balloon was then withdrawn until proximal to the DES and inflated to between 0.4 and 0.7 atm. Physiological saline was then injected downstream of the occlusion balloon via its coaxial catheter; 30 mL were injected during each pullback. OCT gives a clear image once the lumen is sufficiently transparent. Automatic light-source pullback then began (1 mm/s, with 15 image/s acquisitions). A 30-mm DICOM-format video recording of the artery was made, including the stented segment. The balloon was then deflated and the saline injection stopped. Several pullbacks were sometimes needed for analysis of the longest stents. Pullback was repeated until perfect visualization of the whole length of all stents was obtained.

Optical coherence tomography analysis

Optical coherence tomography images were selected from the DICOM pullback recordings every millimetre (every 15 images) over the entire stented segment and were analysed by two independent operators (Fig. 1).

Each strut was classified into one of four categories:

- well apposed to vessel wall with apparent neointimal coverage (A);
Population characteristics are given in Table 1. The 25 patients (mean age, 59.7 ± 10.1 years) were stented at severe coronary stenosis sites (77.5 ± 8.9% diameter stenosis on QCA). Minimum lesion diameter and length were 0.67 ± 0.29 mm and 14.45 ± 5.68 mm, respectively, with a reference diameter of 2.99 ± 0.33 mm.

A total of 42 ZESs (1.68 per patient) were implanted in de novo lesions, with good initial angiographic results. Stent diameter ranged from 2.5 to 4.0 mm (mean, 3.01 ± 0.34 mm) and length ranged from 8 to 30 mm (mean, 18.40 ± 6.30 mm). Implantation used a mean balloon pressure of 14.0 ± 2.4 atm, usually without predilatation (81%). Mean acute gain was 2.25 ± 0.34 mm.

Clinical and angiographic follow-up

There were no complications secondary to angioplasty during the 6-month follow-up period under dual antiplatelet therapy or during the OCT procedure.

At 6 months, there were no intrastent binary restenoses (angiographic diameter stenosis > 50%) requiring further revascularization. Mean restenosis diameter was 20.2 ± 8.7% with a mean late-loss of 0.52 ± 0.30 mm on QCA.
Optical coherence tomography analysis

Optical coherence tomography was feasible in all 25 patients and 69 pullbacks were performed to analyse the 42 stents (1.64 per stent). In all, 745 mm of stent were studied, and 10,169 struts were visualized. Strut coverage thickness was assessed by two independent operators. Concordance on quantitative measurements was virtually perfect, with an intraclass correlation coefficient of 0.99. The value submitted for analysis was the mean of the two observers’ estimates. Strut coverage was likewise classified in the four exclusive categories by the two independent observers, again with virtually perfect agreement (kappa = 0.99). In case of disagreement, the category to be adopted for analysis was determined by a third observer. Results are shown in Table 2.

Neointimal hyperplasia

Mean stent area was 8.31 ± 2.15 m² and mean lumen area was 5.46 ± 2.17 mm². Mean NIH area was 2.85 ± 0.82 mm², with a percentage obstruction of 36.1 ± 12.3%. Considering lumen area and stent area as disks, with diameters calculated as diameter = 2*√(area/π), mean stent diameter, lumen diameter and NIH thickness were 3.22 ± 0.41 mm, 2.57 ± 0.52 mm and 0.65 ± 0.23 mm, respectively. Mean coverage thickness measured on each strut (n=10,169) was 333 ± 147 µm for 42 ZESs.

Neointimal strut coverage

The incidence of non-covered struts was very low at 6 months (111/10,169; non-covered strut ratio = 1.1%). Only 65 struts were observed to be remote from the coronary wall because of malapposition (0.5%) or a collateral branch (0.2%). On most slices, all struts were covered (699/745, 93.8%). No thrombi were observed in any of the 42 stents.

The rate of cross sections with a non-covered strut ratio > 0.3 was very low (6/745, 0.8%). On the 745 slices, a converse relation was also found between non-covered strut ratio and strut coverage thickness or NIH percentage obstruction (Fig. 2).

Spatial distribution of neointimal hyperplasia

Fig. 3 shows mean stent area, lumen area, NIH area, strut coverage thicknesses, NIH obstruction and non-covered strut ratio on the 745 slices and in each segment. There were no significant differences in longitudinal distribution with regard to any of the criteria studied (p > 0.05).

Table 2 Results of optical coherence tomography analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>QCA data</th>
<th>OCT data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference lumen diameter</td>
<td>Lumen area (mm²)</td>
</tr>
<tr>
<td></td>
<td>(mm)</td>
<td>5.46 ± 2.17</td>
</tr>
<tr>
<td>Minimum lumen diameter (mm)</td>
<td>2.40 ± 0.46</td>
<td></td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>20.2 ± 8.7</td>
<td></td>
</tr>
<tr>
<td>Late-loss (mm)</td>
<td>0.52 ± 0.30</td>
<td></td>
</tr>
<tr>
<td>Stents (n = 42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area (mm²)</td>
<td>8.31 ± 2.15</td>
<td></td>
</tr>
<tr>
<td>Stent area (mm²)</td>
<td>5.46 ± 2.17</td>
<td></td>
</tr>
<tr>
<td>NIH area (mm²)</td>
<td>2.85 ± 0.82</td>
<td></td>
</tr>
<tr>
<td>NIH obstruction (%)</td>
<td>36.1 ± 12.3</td>
<td></td>
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<tr>
<td>Lumen diameter (mm)</td>
<td>2.57 ± 0.52</td>
<td></td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.22 ± 0.41</td>
<td></td>
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<tr>
<td>NIH thickness (mm)</td>
<td>0.65 ± 0.23</td>
<td></td>
</tr>
<tr>
<td>Cross sections (n = 745)</td>
<td>Number of cross sections per stent</td>
<td>17.7 ± 5.7</td>
</tr>
<tr>
<td></td>
<td>Cross sections with all covered struts</td>
<td>699 (93.8)</td>
</tr>
<tr>
<td></td>
<td>Cross sections with non-covered struts</td>
<td>23 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Cross sections with malapposed struts</td>
<td>11 (1.5)</td>
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<tr>
<td></td>
<td>Cross sections with struts facing a collateral branch</td>
<td>12 (1.6)</td>
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<tr>
<td></td>
<td>Cross sections with thrombus</td>
<td>0 (0)</td>
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<td></td>
<td>Cross sections with non-covered strut ratio &gt; 0.3</td>
<td>6 (0.8)</td>
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<tr>
<td>Struts (n = 10,169)</td>
<td>Number of struts per stent</td>
<td>242.1 ± 92</td>
</tr>
<tr>
<td></td>
<td>Covered struts</td>
<td>10058 (98.9)</td>
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<tr>
<td></td>
<td>Non-covered struts</td>
<td>46 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Malapposed struts</td>
<td>47 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Collateral struts</td>
<td>18 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Coverage thickness per strut (µm)</td>
<td>333 ± 147</td>
</tr>
</tbody>
</table>

NIH: neointimal hyperplasia; OCT: optical coherence tomography; QCA: quantitative coronary angiography. Data are number (%) or mean ± standard deviation.
Mean cross-sectional NIH heterogeneity was very low (0.375 ± 0.107). No longitudinal effect was found on this criterion (p = 0.662), suggesting a high level of longitudinal NIH homogeneity.

Discussion

Optical coherence tomography is a particularly effective, high-resolution, imaging technique for analysing the more superficial coronary layers and controlling stenting. The present study confirms the feasibility of the technique in selected lesions and the good reproducibility of its qualitative and quantitative analysis of neointimal stent coverage. All 42 stents initially selected for control were analysed.

Previous angiographic findings showed greater late-loss after implantation of a ZES compared with a first-generation DES (SES or PES). In 11 randomised trials, Pocock et al. reported a late-loss of less than 0.21 mm with SESs, between 0.30 and 0.49 mm with PESs, between 0.60 and 0.61 mm with ZESs, and between 0.80 and 1.06 mm with bare-metal stents [17].

Comparative OCT studies have confirmed greater NIH after ZES implantation. Kim et al. [18] observed a mean NIH thickness of 251.2 vs 85.5 μm (p < 0.001) and a percentage NIH area of 27.9 vs 11.2% (p < 0.001) at 9 months with ZESs and SESs, respectively. In a previous study [19], we found a significant difference between ZESs and PESs: mean strut coverage thickness 333 vs 154 μm (p < 0.001) and percentage NIH area 38 vs 17% (p < 0.001), respectively.

Figure 3. Spatial distribution of neointimal hyperplasia (NIH) and strut coverage, 6 months after zotarolimus-eluting stent implantation (n = 42), from quantitative optical coherence tomography analysis. A. Mean stent area, NIH area (NIHA) and lumen area (LA) (mm²) in all 745 slices; mean areas in five longitudinal stent segments (P2: proximal; P1: proximal-medial; M: medial; D1: distal-medial; D2: distal). B. Mean strut coverage thickness (μm) in all cross sections and in five longitudinal stent segments (bars), and neointimal hyperplasia (NIH) percentage obstruction (points). C. Mean non-covered strut ratio in all cross sections and in five longitudinal stent segments.
Guagliumi et al. reported a similar difference in the ODESSA trial [20], in which 77 patients (189 stents) were randomised and monitored by OCT 6 months after long-lesion stenting requiring overlapping stents: mean percentage NIH was 19.3% with SESs, 31.5% with PESs, 45.2% with ZESs and 57.8% with bare-metal stents.

The present mean 0.333 mm strut coverage thickness (to be multiplied by two to obtain the OCT diameter late-loss value) agrees with the late-loss values reported in the ENDEAVOR II and IV studies (0.61 and 0.67 mm, respectively [21]). It was noteworthy that coverage thickness was independent of stent diameter or length (Fig. 4), making percentage obstruction greater with small-diameter stents (Fig. 4D); with a constant strut coverage thickness of 0.333 mm, obstruction with a 2.5 mm diameter stent theoretically approximates 50%.

ZES strut coverage was virtually complete by 6 months. In other series [18—20], as in the present, no thrombi were ever reported and ZES strut coverage was almost total on OCT. First-generation DES coverage was less at 6 or 9 months, with 8 to 12% of SES struts remaining non-covered [14,18,20], and was still incomplete at 24 months (5% non-covered SES struts) [22].

The originality of the present study lay in its analysis of the spatial distribution of NIH at six months post stenting. NIH proved homogeneous in terms of both coverage thickness and non-covered strut ratio, longitudinally and axially. There were no significant differences between the five longitudinal stent segments, while NIH variability was very low on all slices. These data suggest that, in the present series, the coronary response to zotarolimus was homogeneous.

Non-uniform NIH was observed in previous intravascular ultrasound studies of SESs, attributed by the authors to possible non-uniform stent distribution, stent under-expansion [23,24] or a heterogeneous local response to the drug [25].

In the present series, the homogeneous reaction may be explained by the non-occurrence of stent under-expansion (confirmed by stent area measurement), lesion selection for OCT feasibility, which excluded more complex plaques, and the absence of overlapping. The specific impact of zotarolimus or of the stent platform will need to be investigated in larger-scale, comparative studies.

Anatomopathology studies reported delayed endothelialization after DES implantation. Post-mortem studies on first-generation DESs found NIH to be sometimes heterogeneous, with a converse relationship between non-covered strut ratio and NIH thickness [11]. Finn et al. reported that a non-covered strut ratio of > 0.30 in a given cross section increased the intrastent thrombosis risk ninefold. The most recent OCT studies have adopted this prognostic index [16,18]. We also found in the present series a relationship between NIH and non-covered strut ratio (Fig. 2).

Deficient strut coverage on OCT can be considered to be a thrombosis risk marker. There is, however, a discrepancy between the rate of non-covered active stents at several months post implantation and the much lower rate of late thrombosis. Such “vulnerable” stents may be at increased risk of thrombosis in case of termination of or resistance to antiplatelet therapy. If a correlation could be demonstrated between OCT findings and large-scale clinical study results, OCT might be able to guide the duration of dual antiplatelet therapy, comparing theoretical late thrombosis risk for the various kinds of stent.

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**Figure 4.** Relationship between mean strut coverage thickness, neointimal hyperplasia (NIH) obstruction measured by optical coherence tomography and stent length (A, B) and stent diameter (C, D), 6 months after zotarolimus-eluting stent implantation (n=42).
**Study limitations**

There are some limitations to this study. The series comprised only 25 patients and analysis concerned only 42 stents. Lesions were selected for OCT (M2 version, LightLab Imaging) feasibility. The most complex stenoses (bifurcations, overlapping, in tortuous or calcified coronary arteries) were excluded. Moreover, despite its good performance, OCT cannot be assimilated to in vivo histology. Certain aspects of coverage may, in fact, be due to fibrin or microthrombus. Conversely, endothelialization may be underestimated on OCT, when thin and translucent.

**Conclusion**

OCT provides precise measurement of NIH volume and stent–strut coverage. The present study found constant, homogeneous NIH, 6 months after ZES implantation. The stent—strut coverage. The present study found constant, OCT provides precise measurement of NIH volume and non-covered strut ratio. There are some limitations to this study. The series comprised only 25 patients and analysis concerned only 42 stents. Lesions were selected for OCT (M2 version, LightLab Imaging) feasibility. The most complex stenoses (bifurcations, overlapping, in tortuous or calcified coronary arteries) were excluded. Moreover, despite its good performance, OCT cannot be assimilated to in vivo histology. Certain aspects of coverage may, in fact, be due to fibrin or microthrombus. Conversely, endothelialization may be underestimated on OCT, when thin and translucent.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


