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Optical coherence tomography characteristics of in-stent restenosis are different between first and second generation drug eluting stents ☆

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ABSTRACT

Aims: Characterization of neointimal tissue is essential to understand the pathophysiology of in-stent restenosis (ISR) after drug eluting stent (DES) implantation. Using optical coherence tomography (OCT), we compared the morphologic characteristics of ISR between first and second generation DES.

Methods and Results: OCT was performed in 66 DES-ISR, defined as >50% angiographic diameter stenosis within the stented segment. Patients with ISR of first generation sirolimus-eluting stents (SES), paclitaxel eluting stents (PES) and second generation zotarolimus-eluting stents (ZES), everolimus-eluting stents (EES) and biolimus-eluting stents (BES) were enrolled. Quantitative and qualitative ISR tissue analysis was performed at 1-mm intervals along the entire stent, and categorised as homogeneous, heterogeneous and neo-atherosclerosis. The presence of microvessels and peri-strut low intensity area (PSLIA) was determined in all ISR. Neoatherosclerosis was identified by lipid, calcium and thin-cap fibro-atheroma (TCFA) like lesions. We compared the two DES generations at both early (<1 year) and late (>1 year) follow-ups.

In second generation DES a heterogeneous pattern was prevalent both before and after 1 year (57.1% and 58.6% respectively). Neo-atherosclerosis was more common in the early period in first generation DES (19.4% vs 11.7%, $p < 0.01$), but after one year was more prevalent in second generation DES (7.0% vs 19.3%, $p < 0.01$). Similar prevalence of TCFAs was observed in both groups in all comparisons.

Conclusions: When ISR restenosis occurs in second generation DES, the current data suggest a different time course and different morphological characteristics from first generation. Future prospective studies should evaluate the relationship between ISR morphology, time course and clinical events.

1. Introduction

Although a significant reduction in the rate of in-stent restenosis (ISR) has been observed with first and second generation (G1 and G2) drug eluting stents (DES) compared with bare metal stents (BMS), this event still limits long term outcomes after percutaneous coronary intervention (PCI) (1,2). However, the basis for this observation is not yet fully understood. Optical coherence tomography (OCT) is the preferred modality to study arterial healing after stent implantation. Due to its high resolution, OCT can disclose plaque morphology with a sensitivity close to histology and provide an accurate assessment of stent deployment, with special focus on the number and distribution of covered struts (3,4). Recently, OCT has been used for the characterization of ISR and different tissue patterns have been described (5,6). Studies of DES-ISR are limited but there is an evidence that neointimal hyperplasia after DES may be more heterogeneous and occur earlier than the fibrotic intimal hyperplasia observed after BMS implantation (7,8). Furthermore, there is a histological evidence of neoatherosclerotic tissue growth, mainly described within first generation DES-ISR, which is characterized by lipid and/or calcium deposition, macrophage infiltration and necrotic core formation. In some cases these lesions are almost indistinguishable from thin-cap-fibro-atheroma (TCFA) lesions found in native plaques (8,9) which are consistently shown to correlate with

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acute coronary events (10–12). G2 DES, probably because of greater biocompatibility, have drastically reduced restenosis and stent thrombosis when compared with G1 DES (13–16). However, ISR has also been described with these new generation devices.

The aim of this study was to compare the morphologic characteristics of neo-intimal tissue in a consecutive series of ISR of G1 and G2 DES studied with OCT.

2. Methods

2.1. Study design and population

All consecutive patients with one or more ISR in a G1 or G2 DES, studied with OCT between January 2007 and December 2012, were considered for the study. ISR was defined as angiographically documented diameter stenosis greater than 50% within the stented segment. The region of interest extended from the distal to the proximal stent edge, excluding the margins. As in previous pathologic ISR studies (8), we considered overlapping and consecutive stents as one lesion, while stents separated by more than 5 mm were considered as separate lesions. Patients included in our study underwent coronary angiography as clinically indicated, due to stable angina or NSTE-acute coronary syndromes, or as elective scheduled angiographic follow-up (because of the type of lesion previously treated [left main or equivalent] or as part of approved DES trials) (17,18). The use of intravascular imaging with IVUS or OCT is routinely practised in our centre to diversify the treatment of ISR based on its prevalent mechanism (underexpansion vs hyperproliferation) as indicated and explained in the informed consent approved by the institutional review board. We excluded patients with total occlusion, ST-segment elevation myocardial infarction, cardiogenic shock, serum creatinine >2 mg/dl and bare metal stent ISR.

2.2. Quantitative coronary angiography

Quantitative coronary angiography (QCA) was performed offline by a skilled analyzer blinded to patients' clinical characteristics and OCT analysis, using dedicated cardiovascular measurement software (QAngio XA 7.1 Medis Medical Imaging System, Leiden, The Netherlands) on a single, selected 2D end-diastolic image frame. Care was taken to select projections and frames with minimal foreshortening and vessel overlap, analyzing the view that revealed the highest degree of stenosis. After careful calibration, lesion length, proximal and distal references, minimal luminal diameter (MLD) and percent diameter stenosis (%DS) were calculated. Based on QCA results, lesions were classified as focal restenosis: <10 mm in length, or diffuse restenosis: >10 mm in length (19).

2.3. Optical coherence tomography imaging and analysis

The OCT images were acquired, using a non-occlusive technique, through a 2.7 Fr C7 Dragonfly Imaging Catheter (LightLab Imaging Inc., Westford, MA, USA), flushed with undiluted contrast dye and calibrated before the acquisition, which was inserted distal to the lesion of interest. A mechanical pullback at a speed of 20 mm/s was started during continuous automatic flushing of 2–5 ml/s of iodixanol (Visipaque™ 320 mg I/ml GE Healthcare, Amersham, UK) to ensure blood clearance from the coronary arteries, using a Medrad injector (Medrad Inc., Warrendale, PA, USA).

Quantitative and qualitative OCT analyses were performed off-line by agreement of two experienced analysts, blinded to clinical and angiographic lesion characteristics using commercial software (LightLab; St. Jude, Minneapolis, MN, USA), at every 1 mm cross section (CS) throughout the pullback from the distal to the proximal stent edge. Quantitative measurements included lumen and stent cross-sectional areas (CSA) (automatically traced and manually adjusted when required), neointimal hyperplasia (NIH) area (stent area–lumen area), percentage of NIH area (NIH area / stent area × 100) (Fig. 1) (20). For this analysis, only CSs with a percentage of NIH area ≥50% have been considered as effective part of the restenotic segment within stent (20).

Owing to a lack of consensus regarding the classification of ISR optical patterns and their histopathological basis, we analysed every evaluable cross section and adopted previously reported qualitative criteria for this analysis (6,9) (Fig. 2): 1) *homogeneous neointima*; 2) *heterogeneous neointima*; and 3) *neo-atherosclerosis*. The homogeneous pattern consists of tissue with uniform optical properties and no focal variation in backscattering. Heterogeneous tissue was identified by the presence of several variations in the optical backscattering properties and sub-classified in: *layered pattern*, consisting in concentric layers with different optical properties (thick adluminal high scattering layer and an abluminal low scattering layer), *patchy pattern*, irregular and highly echo-lucent regions throughout the layers, and *speckled pattern*, restenotic tissue with heterogeneous speckled bands (6,21). We defined neo-atherosclerosis as ISR showing optical areas consistent with at least one of the following features: *lipids*, diffusely bordered, signal-poor regions; *calcium* as well-delineated, low back-scattering heterogeneous regions; and *thin-cap fibro-atheroma* (TCFA) plaques, with a fibrous cap thickness ≤65 μm and an angle of lipid tissue ≥180 showing relevant signal attenuation (3,22). In these neo-atherosclerotic lesions, we also identified the presence of *macrophages*, multiple strong back reflections, resulting in a relatively high OCT signal variance within the fibrous cap (23). Hence, in the presence of the well defined neo-atherosclerotic features reported above, we classified the ISR as *neo-atherosclerosis*, while we defined the *heterogeneous* group as those with an ISR optical pattern which was neither homogeneous nor neoatherosclerotic tissue.

Furthermore, in all lesions we identified the presence of: *microvessels*, low backscattering structure with a diameter <200 μm; *peri-strut low intensity area* (PSLIA) defined as a region around stent struts with homogeneous lower intensity than surrounding tissue, without signal attenuation (24); *malapposed struts*, when the axial distance from DES strut to the luminal surface was longer than the strut/polymer thickness (25), excluding bifurcations; and *uncovered struts*, NIH thickness equal to 0 μm (26).

The decision to perform a dilatation before proceeding to OCT acquisition was left to the operator's discretion on the basis of the angiographic findings. In the event of a tight ISR lesion, pre-dilation with a 2.0 semi-compliant balloon, inflated at nominal pressure was allowed. Since balloon inflation may create a rupture of the fibrous cap, we excluded from our analysis disrupted intima like lesions and the presence of intraluminal material.

2.4. Statistical analysis

Categorical variables are expressed as numbers (percentages) and comparisons between groups were performed with χ^2 or Fisher's exact test. Continuous variables are expressed as the mean ± standard deviation and compared with Independent T-test. The primary analysis compared ISR characteristics at early follow-up (less than 1 year) and late follow-up (more than 1 year) within the first or the second generation groups. Next, the comparison was performed between generations, within the early or late period (20). A p value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software (SPSS Inc. Version 20, Chicago, Illinois).

2.5. Results

A total of 66 ISR lesions were identified in 41 consecutive patients enrolled in this study. We found 44 ISR within G1 DES: 21 sirolimus-eluting stents (SES) (Cypher SELECT, Cordis, Miami Lakes, FL, USA) and 23 paclitaxel-eluting stents (PES) (Taxus EXPRESS and Liberté, Boston Scientific, Natick, MA, USA). We also identified 22 ISR lesions in G2 DES: of which 11 everolimus-eluting stents (EES) (9 Xience, Abbott Vascular, Santa Clara, CA, USA; and 2 Promus, Boston Scientific,