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Mechanisms of balloon angioplasty and repeat stenting in patients with drug-eluting in-stent restenosis ☆

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ABSTRACT

Background: Mechanisms of lumen gain during reinterventions in patients with drug-eluting stent (DES) in-stent restenosis (ISR) remain unsettled.
Methods: We sought to assess the mechanisms of acute lumen gain after balloon angioplasty (BA) and repeat drug-eluting stent (DES) implantation in patients with DES-ISR. Following a prospective protocol 29 consecutive patients with DES-ISR were sequentially treated with BA and new DES implantation under a multimodality intracoronary imaging assessment including intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Imaging studies were systematically obtained, at baseline, after BA, and after DES. Results of interventions were compared using volumetric and morphometric (ISR pattern and injury score) analyses.
Results: IVUS and OCT demonstrated that acute lumen gain after BA and DES equally results from a reduction in intra-stent neointimal volume and further DES expansion. As compared with BA, repeat DES implantation not only increased final lumen (baseline 39.6 ± 18.5 mm^3, post-BA 58.6 ± 26.6 mm^3, post-DES 84.2 ± 30.8 mm^3, all $p < 0.001$) but also provided a smoother lumen (injury score 1.57 ± 0.86 vs 0.22 ± 0.26, $p < 0.001$). At the 9th month of angiographic follow-up (86% patients) in-stent late loss was 0.44 ± 0.5 mm and 4 patients (16%) developed ISR. The ISR pattern on OCT was not associated with the injury score after interventions or late angiographic findings. Likewise, the injury score did not predict late angiographic outcome.
Conclusions: In patients with DES ISR, lumen gain equally results from a reduction in intra-stent neointimal volume and further DES expansion. As compared with BA, repeat DES implantation provides a larger and smoother coronary lumen.

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1. Introduction

Drug-eluting stents (DESs) are widely used during coronary interventions [1]. Although DES markedly inhibit neointimal proliferation, in-stent restenosis (ISR) may still occur after DES implantation [2,3]. In fact, treatment of DES-ISR remains not only a challenge but also a significant clinical problem [2,3]. Indeed, the strategy of choice in these patients currently remains unsettled [2,3]. Although the acute results obtained with diverse therapeutic modalities are largely favorable, the long-term angiographic and clinical outcome of patients treated for DES-ISR remains relatively poor [4–10]. Therefore, additional insights on the mechanisms of lumen gain during these interventions are required to further optimize procedural results and, eventually, late clinical outcomes.

Intravascular ultrasound (IVUS), and more recently optical coherence tomography (OCT), are widely used in the diagnosis and management of DES-ISR [11–14]. However, scarce information is available on the potential value of these imaging techniques to assess and compare the results of different interventions. In this prospective study we sought to assess the mechanism of lumen gain after balloon angioplasty (BA) and repeat DES implantation in patients undergoing reinterventions for DES-ISR. Procedural results were systematically analyzed using morphometric and volumetric analyses following a multimodality intracoronary imaging protocol that combined IVUS and OCT imaging.

2. Methods

2.1. Patients and study protocol

This study represents a prospective "mechanistic study" designed within the **R**estenosis **I**ntra-stent: **B**alloon angioplasty vs drug-eluting **S**tent implantation (**RIBS**) initiative,

☆ All the above authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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previously described in detail [6,7]. Inclusion and exclusion criteria were similar to those used in the RIBS randomized studies [6,7]. In brief, patients with DES-ISR (>50% diameter stenosis on visual estimation) with angina or documented ischemia were eligible. Patients with DES-ISR on small vessels (≤2.0 mm) or with very long lesions (>32 mm in length) were excluded. Patients presenting within the first month after DES implantation and those with an acute myocardial infarction or intracoronary thrombus were also excluded [6,7]. Patients with edge-ISR [15] were only eligible when intracoronary imaging techniques demonstrated that the stent margin was actually involved. Patients with contraindications to aspirin or clopidogrel treatment, severe renal failure, peripheral vascular disease or major concomitant systemic diseases were also excluded.

All patients in this study were enrolled at the Clínico San Carlos University Hospital in Madrid, the coordinating center for the RIBS studies. The study was performed according to the provisions of the Declaration of Helsinki. The use of combined IVUS and OCT imaging in these patients was part of the RIBS protocol that was approved by the Institutional Ethics Committee. Informed consent was obtained from all patients.

2.2. Coronary interventions

Patients were pre-treated with aspirin and clopidogrel. Before interventions a bolus of unfractionated heparin (100 mg/Kg) was given with additional boluses along the procedure as required according to the activated clotting time (target >250 s). OCT and IVUS imaging were systematically performed: a) at baseline, b) after BA and c) after DES implantation. In cases with tight ISR a balloon catheter could be advanced across the lesion (but not inflated) to facilitate the subsequent advancement of the imaging catheters prior to intervention.

BA was performed according to standard techniques for patients with ISR [6,7]. Special care was taken during balloon inflation to avoid injuries at adjacent coronary segments and to prevent "watermelon seeding" phenomena. Accordingly, balloons were carefully inflated under fluoroscopic visualization to ensure that balloon slippage did not occur. If required, an additional guidewire was advanced in parallel (buddy wire technique) to stabilize the balloon at the target site. No patient required lesion dilation with a cutting balloon. Once the correct balloon inflation at the target site was confirmed relatively high pressures (>14 bar) were recommended. The use of a balloon-to-artery ratio of 1.1 (visual assessment) was suggested. Whenever residual waists on the balloon were noticed aggressive dilations with non-compliant balloons were performed to tackle underlying DES underexpansion. Each balloon inflation, with its corresponding pressure, was recorded. The angiographic result of BA was considered as adequate when residual stenosis on visual assessment was <20%. IVUS and OCT imaging were repeated after the last BA dilation.

Subsequently, stent implantation with a new DES was performed. The selection of the specific DES to be implanted was left to the operator's criteria. Special attention was paid to ensure complete lesion coverage and to prevent geographic-miss related problems [7]. Again, high pressures were recommended. Post-dilation with non-compliant balloons was always performed whenever suboptimal results or underexpansion was detected on angiography. The precise final post-dilation strategy was left to the operator's criteria and no predefined IVUS or OCT end-points were mandated to optimize final results. IVUS and OCT imaging were repeated after the last balloon postdilation.

Following interventions serum cardiac troponin and creatine kinase levels (MB when abnormal) and 12-lead electrocardiograms were serially obtained for 24-hours [6,7]. After discharge all patients received aspirin indefinitely and clopidogrel for 1 year. In all patients an angiographic evaluation was scheduled at 9-months but this was performed earlier if clinically indicated. Clinical events during follow-up (death, myocardial infarction, target lesion revascularization) were analyzed using standard definitions as previously reported [6,7]. Stent thrombosis was defined following the Academic Research Consortium criteria [16].

2.3. Angiographic analyses

Coronary angiograms were analyzed in a core laboratory by trained personnel using standard methodology [6,7,17]. ISR lesion morphology was assessed using Mehran classification [18]. A validated, automatic, edge-detection system (CASS II System, Pie Medical, Maastricht, The Netherlands) was used for quantitative coronary angiography. Selected views (at least 2 orthogonal projections) were obtained after intracoronary nitroglycerin administration (200 μg) at baseline, after BA, after final DES dilation. The same views were recorded at follow-up. Quantitative measurements encompassed the in-lesion and in-segment (treated segment plus 5-mm segments on both sides) analyses [7].

2.4. Intravascular ultrasound

IVUS imaging was obtained with mechanical catheters (Atlantis SR Pro, 40-MHz catheter; Boston Scientific, Fremont, CA) that were advanced 10 mm beyond the distal edge of the stent. A motorized pullback (0.5 mm/s) was obtained until the coronary ostium. Residual neointima and intrastent or edge-dissections were defined using standard criteria [19,20]. Offline quantitative IVUS analysis was obtained with a validated system (QIVUS, Medis, Leiden, The Netherlands). The lumen, stent, neointima (stent minus lumen) and total vessel areas were measured at 1-mm intervals to allow subsequent volumetric analysis [7,20]. In patients with edge-ISR an additional analysis was performed including the lesion extending outside the stent. In this extended (in-segment) analysis the lumen, the adventitia and the plaque burden (total vessel minus lumen) outside the stent were also measured. IVUS imaging was performed before intervention, after BA and after repeat DES. To allow precise sequential analysis and comparisons these three pullbacks were carefully matched to obtain identical segment lengths using the proximal or distal stent edge as a landmark.

2.5. Optical coherence tomography

OCT was performed with time-domain systems (6 patients) (Image wire, M3, Light Lab Imaging, Inc, Westford, MA, USA) or Fourier-domain (frequency domain) systems (23 patients) (C7-XR, Dragon Fly, Light Lab, St. Jude Medical, St Paul, MN, USA). The proximal radiopaque marker of the OCT catheter was advanced beyond the distal stent edge and then a pullback (20 mm/s with frequency domain systems) was obtained using the nonoclusive technique [20,21]. If blood clearance was inadequate or part of the stent was not properly visualized the pullback was repeated after the adequate adjustments in flushing parameters or probe position. OCT images were jointly evaluated by 2 experts. The neointimal tissue pattern was classified by OCT at the site with the minimal lumen area as homogeneous or heterogeneous (including a layered appearance) and as bright or dark, as previously reported [13]. Likewise, the lumen was classified as smooth or irregular and the presence of intraluminal material was recorded. In addition, the presence of neointimal disruptions or dissections was carefully analyzed as a measure of tissue injury. The deepest dissection and the total length of the segment showing dissections were measured. A "neointimal injury score" was calculated (0/absence of dissection, 1/minor [<300 μm in depth] and 2/major dissections [≥300 μm in depth]), at the 4 quadrants of each image (total injury score by frame from 0 to 8). The score was calculated at 1 mm intervals along the total stent length. Subsequently, a global (stent level) neointimal injury score was calculated as a mean of the injury score of individual frames (also from 0 to 8). To assess reproducibility of this score 25 randomly selected OCT frames from different patients were reevaluated 1 month later. Off-line quantitative OCT analyses were performed using dedicated proprietary software (LightLab Imaging) [13,20]. The Z-offset calibration was adjusted before measurements. OCT findings were carefully analyzed for the entire longitudinal extent of the stent. OCT imaging was repeated after BA and also after DES implantation.

2.6. Main outcome measures

The main "quantitative" outcome measure was the volumetric analysis of lumen, stent and neointimal changes after BA and repeat DES implantation by IVUS and OCT. The main "qualitative" outcome measure was the correlation between the neointimal injury induced during the sequential treatment and a) the ISR pattern and b) the acute and late results. Secondary endpoints included acute and long-term angiographic findings and a combined clinical end-point (cardiac death, myocardial infarction and target lesion revascularization).

2.7. Statistical analysis

Categorical data were compared with the Chi-square test or the Fisher's exact test. Continuous data are presented as mean (±SD) or median (IQR) values according to data distribution (Kolmogorov–Smirnov test). The Student's t test (paired or unpaired as indicated) or the Mann–Whitney tests were used to compare continuous variables. The Pearson correlation coefficient was used to assess correlation of continuous variables. Reproducibility of OCT-derived neointimal injury was assessed using a weighted Kappa. Kaplan Meier curves were constructed to determine the event-free survival. The SPSS (V15) statistical package was used. Statistical significance was set at $p < 0.05$.

3. Results

Twenty-nine consecutive patients with DES ISR were prospectively enrolled in the study. All these patients were successfully treated with BA and then with DES under combined (OCT and IVUS) intracoronary imaging. Figs. 1–3 illustrate representative images at baseline and after the sequential treatment strategy. Baseline clinical, angiographic and procedural characteristics are summarized in Table 1. Most lesions were located in the left anterior descending coronary artery and had a focal pattern that frequently involved the stent edge. Most patients presented with ISR of an everolimus-eluting stent ISR and this DES was also the most frequently used during reinterventions. High final dilation pressures were systematically used (Table 1).

Results of quantitative coronary angiography before intervention, after BA and after repeated DES implantation are shown in Table 2. Minimal lumen diameter significantly increased after BA but a significant additional increment was noticed after DES implantation. Late angiographic follow-up was obtained in 25 patients (86%). Angiographic restenosis was found in 4 patients (16%) (Table 2).

OCT results, at baseline, after BA and after DES (matched in-segment analysis) are presented in Table 3. IVUS findings at corresponding matched segments are summarized in Table 4. Both techniques