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Original article

Characterization of in-stent neointimal tissue components following drug-eluting stent implantation according to the phase of restenosis using a 40-MHz intravascular ultrasound imaging system

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ABSTRACT

Background and purpose: It is known that drug-eluting stents (DESs) are associated with in-stent restenosis (ISR). However, the characteristics of neointimal tissue components according to the mechanism and time course of DES ISR have not been fully examined. The aim of this study was to characterize the in-stent neointimal tissue components according to the phase of restenosis using radiofrequency signals from 40-MHz intravascular ultrasound (IVUS), called iMAP-IVUS (Boston Scientific Corp., Fremont, CA, USA).
Methods: IVUS examinations were performed in 37 angina patients (37 lesions) who underwent repeated percutaneous coronary intervention (PCI) for the treatment of DES ISR. The patients were divided into two groups according to the phase of restenosis: the early ISR group (E-IRS; ≤1 year) and the late ISR group (L-ISR; >1 year).
Results: There were 18 patients in the E-ISR group and 19 patients in the L-ISR group. The mean follow-up period between stent implantation and repeated PCI was 8.0 ± 2.2 months in the E-IRS group and 40.4 ± 23.9 months in the L-ISR group. The percentage of lipid components and relative necrotic volume were greater in the L-ISR group than in the E-ISR group (5.77 ± 1.81% vs. 4.51 ± 1.71%, $p < 0.05$ and 12.20 ± 2.97% vs. 8.61 ± 2.33%, $p < 0.001$, respectively). Furthermore, there was a positive correlation between the follow-up duration after DES implantation in the L-ISR group and the presence of a necrotic plaque component ($r = 0.49$, $p < 0.05$).
Conclusions: There were differences in the neointimal plaque characteristics after DES implantation according to the phase of restenosis. This information may lead to a better understanding of the mechanisms of DES ISR.

Introduction

The use of drug-eluting stents (DESs) has remarkably reduced the rate of angiographic restenosis and target lesion revascularization (TLR) compared with that of bare-metal stents (BMSs) [1,2]. However, there continues to be a low rate of in-stent restenosis (ISR) after DES placement, and its prevalence is not negligible because the population treated with DES is large. The mean time from the first percutaneous coronary intervention (PCI) to the detection of ISR related to DES is approximately 12 months, and the duration of ISR after DES implantation is longer than that observed after BMS implantation [3]. The precise reasons why DES restenosis occurs remain unknown; however, some mechanisms of ISR after DES implantation have been proposed. Possible reasons, such as biological factors, mechanical factors, and technical factors can be used to predict DES ISR [4]. In addition, previous anecdotal clinical experience has provided evidence of late ISR occurring over 1 year after DES implantation, the so-called "late catch-up phenomenon" [5]. However, the characteristics of neointimal tissue components according to the mechanism and time course of DES ISR have not been fully examined.

iMAP-intravascular ultrasound (IVUS) (iMAP, Boston Scientific Corp., Fremont, CA, USA) is an IVUS imaging system used for tissue characterization with 40-MHz radiofrequency [6]. The iMAP software program (QIvus 2.0, Medis Medical Imaging Systems bv, Leiden, The Netherlands) converts the signal pattern into a frequency spectrum and then compares it with the spectra obtained from various tissues at autopsy (data library) to find the closest

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match. Since the different tissue types (fibrotic, lipidic, necrotic, and calcified) have distinctive spectra, iMAP technology can identify tissues from the frequency spectrum that most closely resemble the tissues obtained on examination [7]. The purpose of this study was to assess the long-term neointimal tissue components after DES implantation using iMAP-IVUS and discuss the mechanisms and time course of DES ISR from the view point of neointimal tissue characterization.

Materials and methods

Study population

In this single-center study, a total of 37 patients were selected from among 53 consecutive patients who underwent elective PCI for DES-ISR and iMAP-IVUS examinations between July 2009 and September 2013. The subjects included patients with stable angina pectoris (SAP) patients (class I or II angina unchanged for more than 2 months) or a positive stress test. The target lesion was ISR after DES implantation (>75% angiographic stenosis based on visual estimation). In total, 16 patients were excluded due to recurrent ISR ($n=6$), stent fracture ($n=4$), visible thrombi on angiography ($n=2$), the inability of the IVUS imaging catheter to cross the ISR lesion into the distal vessel even when pre-dilatation was performed with a small balloon ($n=2$), detection on routine follow-up angiography ($n=1$), and inadequate IVUS imaging quality ($n=1$). No patients were excluded as a result of stent malapposition, ISR due to stent gap, and duration of 30 days or less after the first stent implantation. As a result, 37 patients (37 vessels) were analyzed. Early ISR (E-ISR) was defined as the first ISR observed within 1 year after DES implantation, whereas late ISR (L-ISR) was defined as the first ISR observed >1 year after DES implantation. Type 2 diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin to lower the blood glucose level, a known fasting blood glucose value of ≥126 mg/dl and/or a postprandial 2-h blood glucose value of ≥200 mg/dl. Hyperlipidemia was defined as a total cholesterol level of ≥220 mg/dl, low-density lipoprotein cholesterol level of ≥140 mg/dl, fasting triglyceride level of ≥150 mg/dl, or medication use. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the use of an antihypertensive drug. The estimated glomerular filtration rate (eGFR) was calculated according to the modification of diet in renal disease (MDRD) equation: $\text{eGFR}\ (\text{ml/min/1.73 m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$ (corrected for females by multiplying with a factor of 0.739) [8]. Approval to conduct this study was obtained from the ethics committee of our institute.

PCI procedure

The patients were pre-medicated with aspirin (100 mg/day) and clopidogrel (75 mg/day) for at least 1 week before the procedure. They received intravenous unfractionated heparin immediately prior to PCI in order to achieve an activated partial thromboplastin time of >250 s. None of the patients were given glycoprotein IIb/IIIa inhibitors because these drugs have not been approved in Japan. First, PCI was performed using the technique of pre-dilatation with shorter balloons, a stent long enough to cover the entire area of balloon injury and post-dilatation within the stented lesions employing short, high-pressure balloons. The implantation of two stents was avoided in order to account for stent gaps, and overwrapping stents were implanted in cases involving implantation of two or more DESs. If the IVUS catheter could not cross the lesion due to severe stenosis or occlusion, dilatation was performed with a small balloon prior to advancing the catheter. The coronary flow before the PCI procedure was evaluated based on the thrombolysis in myocardial infarction (TIMI) grade [9]. The pattern of ISR was described using the Mehran classification [10].

IVUS imaging and analysis

IVUS was performed before PCI and after the intracoronary administration of 125–250 μg of nitroglycerin. The data were acquired using a 40-MHz IVUS catheter (Atlantis SR Pro, Boston Scientific). The catheter was advanced beyond the target lesion, and imaging was performed during automatic pullback at a speed of 0.5 mm/s. The IVUS data were stored on a hard disk for an off-line analysis, which was performed independently by two experienced analysts who were unaware of the angiographic findings or baseline clinical and lesion characteristics. The first observer repeated a blind analysis of all the data at two separate time points (with an interval of at least 1 month between the two analyses). A quantitative analysis of the gray-scale IVUS images was performed according to the criteria of the American College of Cardiology Clinical Expert Consensus Document on IVUS [11]. The lesions were qualitatively analyzed using the iMAP software program. The external elastic membrane (EEM), stent and lumen cross-sectional area (CSA) were measured. Using the iMAP software program, the contours of the EEM, stent, and lumen interface were detected semiautomatically. The neointimal plaque CSA was calculated as the stent CSA minus the lumen CSA, and the neointimal plaque burden was calculated as the neointimal plaque CSA divided by the stent CSA. The region of interest was placed between the luminal border and the inner border of the struts to avoid stent strut artifacts (Fig. 1A and B). The minimum lumen site of the culprit lesion was identified based on axial and longitudinal plaques. If there were several slices with equal lumen sizes, the one with the largest EEM and plaque CSA was selected. The lesion length was defined as the segment between the distal to proximal reference sites that appeared normal within an area 5 mm proximal and distal to the lesion. The proximal and distal references were the single slices with the largest lumen and the smallest plaque burden within an area 5 mm proximal and distal to the lesion, before any large side branch. Once a complete set of CSA measurements and the lesion length were obtained, the volumetric analysis was performed automatically.

iMAP-IVUS tissue characterization

The iMAP-IVUS analysis classified the plaques into four tissue components and produced color images (green for fibrotic plaque, yellow for lipidic plaque, red for necrotic plaque, and blue for calcified plaque) (Fig. 1A and B). The absolute plaque area (mm^2), plaque volume (mm^3), and percentage of each tissue component were determined. The percent plaque volume was defined as the ratio of each plaque volume to the neointimal plaque volume (%fibrotic, %lipidic, %necrotic, and %calcified). Using the iMAP software program, we traced the EEM, stent, and lumen CSA semiautomatically, while also analyzing tissue characteristics and calculating the absolute plaque area (mm^2), plaque volume (mm^3), and percentage of each tissue component automatically. In addition, the plaque that was unsuitable for the analysis due to acoustic shadowing behind calcification or a wire artifact was removed automatically.

The application of iMAP-IVUS for tissue characterization has not yet been validated for use with in-stent neointimal tissue. However, we substituted the above four tissue components for the in-stent neointimal tissue. The intra-observer variability yielded good concordance for the plaque volume and plaque components on iMAP-IVUS: $r=0.94$ for plaque, $r=0.93$ for the necrotic component. The inter-observer variability was acceptable: $r=0.88$ for the lumen and $r=0.82$ for the necrotic component.