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Original article

Relationship between optical coherence tomography-defined in-stent neoatherosclerosis and out-stent arterial remodeling assessed by serial intravascular ultrasound examinations in late and very late drug-eluting stent failure

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ABSTRACT

Background: Little is known regarding the association between chronological out-stent vessel remodeling and in-stent tissue characteristics of drug-eluting stent (DES) failure. We aimed to evaluate the relationship between serial vessel remodeling after DES implantation and neoatherosclerosis (NA) assessed by optical coherence tomography (OCT) in patients with DES failure.

Methods: Forty-eight patients with late and very late stent failure after DES implantation, who underwent intravascular ultrasound (IVUS) at both the initial percutaneous coronary intervention and the time of stent failure and OCT imaging at the time of stent failure, were retrospectively investigated. NA on OCT was defined as neointimal formation with the presence of lipids or calcification inside the stents. Lesions were divided into two groups: those with NA and those without NA (NA: $n = 21$; non-NA: $n = 27$). From the serial IVUS examinations, external elastic membrane (EEM) volume and out-stent plaque volume were normalized by stent length and their changes were compared between the two groups.

Results: The NA group showed older stent age [median, 5.1 years (IQR, 4.8–8.3) vs 1.4 years (IQR, 0.8–4.5); $p < 0.01$] and more prevalent sirolimus-eluting stents (SES; 81.0% vs. 29.6%; $p < 0.01$). IVUS findings of the NA group showed a greater serial increase in both normalized EEM volume and normalized out-stent plaque volume (OSPVI) [1.05 (0.41–1.90) vs. 0.11 (−0.64 to 0.80) mm^2; $p < 0.01$; and 0.88 (0.57–1.98) vs. 0.12 (−0.41 to 0.78) mm^2; $p < 0.01$]. On multivariate analysis, percentage change in OSPVI (OR, 1.07; 95% CI, 1.01–1.14; $p = 0.02$) and SES (OR, 9.78; 95% CI, 2.20–43.40; $p < 0.01$) remained independent predictors of NA.

Conclusions: NA in late and very late DES failure was associated with out-stent positive vessel remodeling. In addition to SES, out-stent progressive positive remodeling may help predict NA in late and very late DES failure.

Introduction

The development of drug-eluting stents (DESs) successfully reduced the risk of repeat revascularization compared with bare metal stents (BMSs), but late and very late stent failure continues to occur due to restenosis and stent thrombosis [1]. Irrespective of the stent generation, clinical trials have shown that the incidence of target lesion revascularization continuously increases over time

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[1–4]. Optical coherence tomography (OCT) characteristics of neointima after DES implantation and type of DESs have been related to late neointimal progression or regression [5,6]. Recent studies of histopathology and intracoronary imaging have shown that neoatherosclerotic changes within the stented segment have been identified as the cause of delayed failure in a non-negligible proportion of patients irrespective of stent type [7–11]. Despite the potential clinical impact of neoatherosclerosis (NA) on long-term clinical events after DES implantation, mechanisms of NA have not been fully clarified, specifically, little is known about the impact of vessel remodeling on the development of NA. Given the histological similarities between native atherosclerosis and in-stent NA, we hypothesized that the presence of NA in the stented segment would be associated with progressive positive remodeling after index stent implantation in late and very late stent failure. Therefore, we sought to investigate the relationship between the presence of OCT-defined NA and serial changes in the vessel size of stented segments in patients with late and very late stent failure in whom intravascular ultrasound (IVUS) examinations were performed both at the time of the index stent implantation and late and very late stent failure.

Methods

Study population

The present study was a retrospective, single-center intracoronary imaging study. The IVUS and OCT registry database of Tsuchiura Kyodo General Hospital was queried to identify patients who presented with late and very late stent failure. Patients were included in the present analysis if they met the following criteria: age $>$ 20 years; late and very late ($>$30 days from implantation) symptomatic DES failure irrespective of clinical presentation; high-quality, automated pullback IVUS images of the entire stented segment immediately after implantation and at the time of stent failure; and sufficient OCT images obtained at the time of stent failure. Exclusion criteria for OCT examination were angiographically significant left main disease; renal insufficiency with a baseline serum creatinine level $>$1.5 mg/dL; cardiogenic shock; and congestive heart failure. Patients with IVUS images demonstrating severe calcification or severe non-uniform rotational distortion were also excluded. Patient baseline characteristics including medical history, clinical, biological, and angiographic data, and recent modifications of medication including antiplatelet therapy were collected. The registry was approved by the institutional review board and written informed consent was obtained for the assessment of stent failure with use of both IVUS and OCT before the procedures, and for the enrollment of the present study before the analysis. The study complied with the Declaration of Helsinki.

Cardiac catheterization and angiographic analysis

Each patient underwent standard selective coronary angiography for assessment of coronary anatomy via the radial or femoral artery using a 6-Fr system during the index stent implantation and at the time of stent failure. Coronary angiograms were analyzed quantitatively using the CMS-MEDIS system (Medis Medical Imaging Systems, Leiden, the Netherlands) to measure lesion length, minimum lumen diameter, reference lumen diameter, and percent diameter stenosis. All the stents were implanted during the index procedures according to the institutional standard protocol for percutaneous coronary intervention and the strategies (including the type of stent) were determined at the operator's discretion.

Analysis of stented segment

The culprit lesion of stent failure was determined by angiography; the stent including the most stenotic site showing the minimal lumen diameter was defined as the culprit stent and selected for subsequent IVUS and OCT analyses, which included serial IVUS examinations immediately after stenting and at the time of stent failure and OCT examination at stent failure.

Intravascular ultrasound analysis

Serial IVUS images were acquired in standard fashion after intracoronary administration of nitroglycerin 200 μg both during index stent implantation (after completion of stent implantation) and at the time of stent failure using automated pullback (0.5 mm/s). A 40-MHz 2.6-Fr catheter (Atlantis Pro or Opticross; Boston Scientific, Fremont, CA, USA) was used for IVUS image acquisition throughout the study period. Quantitative IVUS analysis of digitized data was performed using off-line software (QIvus software; Medis) for the stent of interest. External elastic membrane (EEM) area, lumen, and stent areas were measured every 0.5 mm. Thereafter, lumen volume (LV), in-stent volume (SV), and vessel volume inside EEM (VV) were computed using Simpson's method (Fig. 1). Furthermore, the following volumetric parameters were subsequently calculated: intra-stent neointimal volume (ISNV = SV–LV) and out-stent plaque volume (OSPV = VV–SV). The serial change of each parameter and the percentage change were calculated as the value at the time of stent failure minus the value immediately after the index stent implantation and divided by the baseline value. Each volumetric parameter was divided by the corresponding stent length to adjust for different stent lengths [volume index (VI)]. To assess chronological out-stent remodeling in the most diseased segment, an additional measurement was separately performed on the cross-sectional images of the minimal lumen area site at stent failure and on the

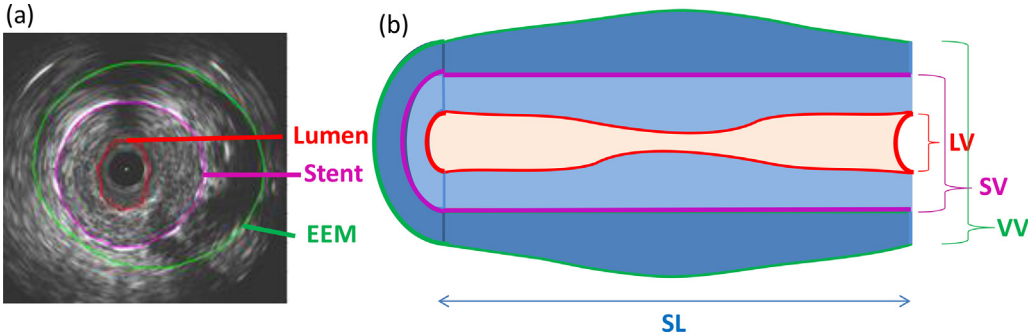

Fig. 1. Volumetric measurements during IVUS analysis. (a) Cross-sectional IVUS analysis. (b) Schematic presentation of volumetric measurement. IVUS, intravascular ultrasound; EEM, external elastic membrane; LV, lumen volume; SV, stent volume; VV, vessel volume in EEM; SL, stent length.

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