Angioscopic Observation of Chronic Neointimal Regression after Endeavor Zotarolimus-Eluting Stent Implantation

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Background: Vascular response after intracoronary bare metal stent (BMS) implantation is biphasic, composed of early restenosis phase and chronic regression phase. The phase transition occurred at around 6 months after stenting. The biphasic vascular response after drug-eluting stent (DES) implantation has not yet been reported so far.

Aim: The aim of this study was to document if chronic neointimal regression occurs after implantation of Endeavor zotarolimus-eluting stent (E-ZES), the second-generation DES.

Methods: Enrolled were 12 E-ZES-implanted lesions without restenosis in 10 patients with coronary heart diseases. Coronary angioscopy was performed twice after stent implantation, at early phase (1–3 years) and chronic phase (3–6 years), to reveal neointimal coverage (NC) on stent struts. NC was semi-quantified from grade 0, no coverage; grade 1, thin coverage; grade 2, thick coverage; and grade 3, invisible stent struts fully embedded into thick neointima. Angioscopy also visualized presence of in-stent yellow plaques (YP) and mural thrombus (MT).

Results: Dominant NC grade at early phase was greater than that at chronic phase (2.91 ± 0.29 vs. 1.83 ± 0.83, P = 0.0008). YP was observed more frequently at early phase than at chronic phase (17% vs. 8%). MT was not detected at both phases.

Conclusions: Chronic neointimal regression occurred after E-ZES implantation although the vascular response to E-ZES progressed more slowly than BMS implantation.

Key words: coronary angiography, neointimal regression, Endeavor zotarolimus-eluting stent

Introduction

Vascular response after intracoronary stent implantation is a healing process of vasculature.1,2 This process is biphasic and composed of early restenosis phase and chronic regression phase after implantation of bare metal stents (BMS).3,4 This phase transition occurs at around 6 months after BMS implantation. In the era of drug-eluting stents (DES), however, in-stent restenosis at 6 months after the implantation is a rare adverse event.5 Thus, we still do not know if and when the biphasic vascular response occurs after DES implantation.

Coronary angioscopy is a unique imaging devise to visualize in-stent appearance, that is, in-stent neointimal coverage (NC), in-stent yellow plaque (YP), and in-stent mural thrombus (MT).6,7 This study aimed to document if and when the biphasic transition occurred from in-stent neointimal growth to its regression after implantation of Endeavor zotarolimus-eluting stent (E-ZES), the second-generation DES.

Methods

Patients and lesions

Enrolled were 12 E-ZES-implanted lesions without in-stent restenosis in 10 patients with coronary heart diseases (three acute coronary syndrome and seven stable angina) (Table 1). Patients underwent twice cardiac catheterization including coronary angiography and angioscopy at early phase (330–950 days) and chronic phase (1014–2070 days after the stent implantation). Interval between the two phases was 1110 days (488, 1673) days as median (minimum, maximum) (Table 2). Enrollment period for the early phase was from 2010 August to 2013 December. That for the chronic phase was from 2013 June to 2016 October. Diabetes mellitus was defined as medication dependent, including oral antihyperglycemic drugs and insulin or as previously known diabetes, that is, fasting plasma glucose concentration >126 mg/dL or plasma glucose concentration >200 mg/dL at any timing. Dyslipidemia was defined as medication-dependent or as previously known dyslipidemia, that is, low-density lipoprotein cholesterol of >140 mg/dL or total cholesterol of >220 mg/dL. Hypertension was defined as medication-dependent or as
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Quantitative coronary angiography (QCA) was performed with an automated edge detection algorithm (CASS 5.9.2, Pie Medical Imaging, Eindhoven, Netherlands). Coronary angiograms were recorded after intracoronary administration of 0.2 mg nitroglycerin. Diameters of guiding catheters were measured to calibrate magnification. In-stent restenosis was defined as a percent diameter stenosis of >50%.

Coronary angiography

Coronary angiography (Visible®, Fibertech, Tokyo, Japan) was performed safely with manual pullback under transparent low-molecular-weight dextran solution flush as described previously. Angiography semi-quantified NC grades on stent struts, that is, grade 0, no coverage, struts barely exposed in the vessel lumen; grade 1, thin coverage, struts visible translucently; grade 2, thick coverage, struts still bulging into vessel lumen and visible translucently; and grade 3, struts embedded in thick neointima and angioscopically invisible. NC was usually heterogeneous through a stent. Dominant, maximum, and minimum NC grades were determined through a stent. Heterogeneity index was defined as maximum–minimum NC grade, to evaluate the heterogeneity of NC. Angioscopy also visualized in-stent MT and YP.

### Table 1  Patient characteristics

| Patient number | Gender (male/female) | Age (y.o.) | ACS | HT | DM | DL | Smoking | DAPT | Anticoagulant | Statin |
|----------------|----------------------|------------|-----|----|----|----|---------|------|--------------|--------|
| 1              | M                    | 69         | +   | +  | +  | +  | +       | +    | -            | +      |
| 2              | F                    | 80         | +   | +  | +  | +  | -       | -    | -            | +      |
| 3              | M                    | 73         | +   | -  | +  | +  | -       | +    | -            | +      |
| 4              | M                    | 73         | -   | -  | -  | +  | +       | -    | -            | -      |
| 5              | M                    | 74         | -   | +  | -  | +  | +       | +    | -            | -      |
| 6              | M                    | 76         | -   | +  | -  | -  | +       | +    | -            | -      |
| 7              | M                    | 79         | -   | +  | +  | -  | +       | -    | -            | -      |
| 8              | F                    | 78         | -   | +  | -  | -  | -       | +    | -            | +      |
| 9              | M                    | 77         | -   | +  | +  | +  | +       | +    | -            | -      |
| 10             | M                    | 74         | -   | -  | +  | +  | +       | -    | +            | +      |
| n (%)          |                      | 3 (30)     | 7 (70) | 7 (70) | 8 (80) | 6 (60) | 10 (100) | 0    | 6 (60)       |        |

Seven patients had undergone DAPT at chronic phase. Three patients underwent single anti-platelet therapy at chronic phase. LDL-C level decreased from 96.0 ± 27.9 at early phase to 83.9 ± 27.4 mg/dL at chronic phase (P < 0.049). Data were given as mean ± SD or n (%). DAPT: dual anti-platelet therapy.

### Table 2  Temporal change of dominant NC grade

| Patient number | Lesion number | Elapse after stenting (days) | Dominant NC grade | DAPT | Anticoagulant | Statin |
|----------------|--------------|-----------------------------|-------------------|------|--------------|--------|
|                |              | Early | Chronic | Early | Chronic |
| 1              | 1            | 379   | 1101    | 3     | 2          |
| 2              | 2            | 366   | 1282    | 3     | 3          |
| 3              | 3            | 366   | 1282    | 3     | 2          |
| 4              | 5            | 364   | 1134    | 3     | 2          |
| 5              | 6            | 442   | 1542    | 3     | 2          |
| 6              | 7            | 352   | 1674    | 3     | 1          |
| 7              | 8            | 526   | 1014    | 3     | 1          |
| 8              | 9            | 330   | 1329    | 3     | 1          |
| 9              | 10           | 950   | 2070    | 3     | 1          |
| 10             | 11           | 565   | 1685    | 2     | 3          |
|                | 12           | 357   | 1546    | 3     | 1          |
| Mean           |              | 448   | 1501    | 2.91†| 1.83       |
| SD             |              | 174   | 349     | 0.29 | 0.83       |

Abbreviations: ACS, acute coronary syndrome; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; Smoking, smoking status; DAPT, dual anti-platelet therapy; Anticoagulant, anticoagulant therapy; Statin, statin therapy.

†P = 0.0008 versus dominant NC grade at the chronic phase. NC: neointimal coverage.
Regression of neoatherosclerosis might be affected by cytosuppressive drug and solvent polymer-induced inflammation. We first reported here the biphasic vascular response after E-ZES implantation, the second-generation DES. QCA failed to detect significant regression of in-stent neointima at chronic phase (Table 3). Coronary angioscopy, a unique imaging device more sensitive to detect in-stent neointimal growth and regression than angiography, revealed the sufficient in-stent NC at early phase and the decrease in NC grade at chronic phase (Figs. 1–2, Tables 2 and 4). The putative phase transition date from proliferation to regression was 931 ± 241 days after stenting (Fig. 2).

The mechanism of this intriguing vascular response has not yet been fully understood. We would propose two hypotheses. First, the chronic neointimal regression we observed in this study would be regression of neatherosclerosis. Neatherosclerosis is pathological diagnosis defined as in-stent neointimal atherosclerotic change which has developed at more than a year after stenting. In clinical settings, neatherosclerosis was diagnosed by coronary angioscopic findings including YP. Regression of neatherosclerosis might be affected by clinical status, for example, statin use. Our intravascular imaging data at early phase, that is, no in-stent restenosis (Table 3) and the low incident rate of YP and MT (Table 4), however, do not support the presence of neatherosclerosis at early phase. Second, the chronic neointimal regression would be a part of vascular healing process after E-ZES implantation. At early phase, stent-related vessel injury induced proliferative activity at vessel wall. At chronic phase, apoptosis played a certain role in reduction of cell number in neointima. The phase transition appeared to occur more slowly after E-ZES implantation than BMS implantation.
and NC grade of C-SES were significantly less than BMS,\(^5,6\) whereas those of E-ZES was similar to those of BMS.\(^13\) Using angioscopy, we have previously demonstrated case reports of a relatively rapid healing process for an E-ZES-related coronary pseudoaneurysm.\(^5,16\) We also reported the good NC at 1 year after E-ZES implantation in patients either with acute coronary syndrome or with stable angina pectoris.\(^9\) These unique features of E-ZES might allow us to detect the biphasic vascular response after stent implantation.

**Table 4** Angioscopic findings

|                      | Early       | Chronic     | P value   |
|----------------------|-------------|-------------|-----------|
| Dominant NC grade    | 2.91 ± 0.29 | 1.83 ± 0.83 | 0.0008    |
| Maximum NC grade     | 2.83 ± 0.39 | 2.16 ± 0.71 | 0.016     |
| Minimum NC grade     | 2.17 ± 0.83 | 1.08 ± 0.28 | 0.0008    |
| Heterogeneity index\(^1\) | 0.67 ± 0.78 | 1.08 ± 0.67 | 0.173     |
| Yellow plaque        | 2 (17)      | 1 (8)       |           |
| Mural thrombus       | 0           | 0           |           |

In all, 12 lesions were observed twice by coronary angioscopy.\(^1\) Heterogeneity index was defined as maximum-minimum NC grade. Data were given as mean ± SD or n (%). NC: neointimal coverage.
The authors have no conflicts of interest to declare.

E-ZES progressed more slowly than BMS implantation. After E-ZES implantation although the vascular response to noninvasive DES.

We conclude that the biphasic transition is a common phenomenon in DES. Further prospective study will be necessary to determine whether the late arterial repair might affect the vascular response after stenting.

There are several limitations in this study. First, this study was a single-center study composed of small number of patients. We analyzed only 12 lesions in 10 patients. Second, coronary angioscopy semi-quantified the neointimal response. Other imaging devices such as optical coherence tomography may provide more precise data. Third, because this study was a retrospective observational study, timings of angioscopic observation after stenting varied within wide range (Table 2). For example, elapsed days after stenting were 950 at early phase and 2070 days at chronic phase in one case, whereas those were 526 at early phase and 1014 days at chronic phase in another case. Fourth, control status of coronary risk factors during follow-up period might affect the vascular response after stenting. Further prospective study will be necessary to conclude that the biphasic transition is a common phenomenon in DES.

In conclusion, chronic neointimal regression occurred after E-ZES implantation although the vascular response to E-ZES progressed more slowly than BMS implantation.

Disclosure Statement
The authors have no conflicts of interest to declare.

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