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Impact of stent over-expansion at distal edge: insights from a 12-month follow-up study

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Abstract. – OBJECTIVE: Although the use of drug-eluting stents has significantly reduced the incidence of restenosis and target lesion revascularization, in-stent and in-segment restenosis remain clinically challenging problems, the underlying mechanisms of which remain unknown. This study aimed to explore the outcomes of different stenting strategies in target vessels with different proximal and distal reference diameters (ΔD ≥ 0.25 mm).

PATIENTS AND METHODS: In this prospective clinical study, 167 patients undergoing percutaneous coronary intervention with ΔD ≥ 0.25 mm according to QCA results were randomized into 2 groups. Group A (n = 85) was treated by a single stent with high-pressure balloon inflation. Group B (n = 82) was treated by a single stent, with high- and low-pressure balloon inflation at the proximal and distal segment, respectively. The target vessel size and late lumen loss were determined by angiographic analysis.

RESULTS: Compared with normal expansion, overexpansion increased the early minimum lumen diameter (A: 2.40 ± 0.18 mm vs. 2.89 ± 0.21 mm; B: 2.45 ± 0.14mm vs. 2.49 ± 0.24 mm, $p < 0.001$), but also increased the percentage of late lumen loss (A: 18.22 ± 0.56%; B: 5.63 ± 0.41%, $p < 0.001$). Although the total restenosis ratio was similar in 2 groups, the incidence of late lumen loss of group A was higher than that of group B.

CONCLUSIONS: Stent overexpansion increased the early minimum lumen diameter, but also increased the occurrence of late lumen loss at the distal edge of the stent.

Key Words:
Angiography, Overexpansion, Restenosis, Late lumen loss.

Abbreviations

PCI = percutaneous coronary intervention; DESs = drug-eluting stents; TLR = target lesion revascularization; SMCs=vascular smooth muscle cells; MLD=minimum lumen diameter; B:A=balloon:artery; ISR=in-stent restenosis; NSTEMI = Non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; QCA = quantitative coronary angiography; MACE = major adverse cardiac events; SES = sirolimus-eluting stents; PES = paclitaxel-eluting stents.

Introduction

In past decades, percutaneous coronary intervention (PCI) had been considered an effective treatment approach for coronary heart disease (CHD). However, restenosis after angioplasty and stent implantation is a serious problem associated with PCI. The use of drug-eluting stents (DESs) has markedly reduced the rates of restenosis and target lesion revascularization (TLR) compared with the use of simple balloon angioplasty and bare-metal stents[1]. Despite the advantages, restenosis remains an issue. Injury of a coronary artery by stenting triggers a series of inflammatory reactions, resulting in the migration and proliferation of vascular smooth muscle cells (SMCs) within the vessel lumen and neointimal hyperplasia[2,3]. Approximately 7-10% of patients treated with DESs experience restenosis and require revascularization[4].

Although many recent studies have tried to address the occurrence, mechanism, predictors, and optimal treatment of restenosis, little is known about the relationship between vascular overexpansion and in-segment or in-stent restenosis. Some studies have concluded that a major determinant of restenosis rate is the final minimum lumen diameter (MLD) achieved after the intervention. Efforts to improve the final MLD include high-pressure balloon inflation and oversized balloons. Several DES trials have demonstrated breakthroughs in the reduction of late restenosis. However, the underlying mechanisms of the process remain unidentified.

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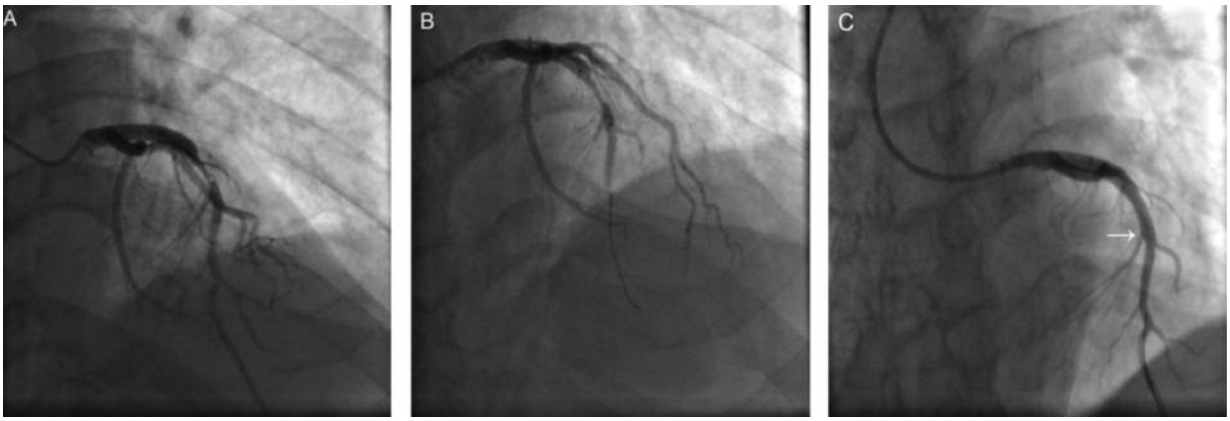

Figure 1. Strategy A: Use of a single stent with high-pressure balloon inflation (balloon-to-artery ratio ≥ 1.2). ***A,*** Pre-stenting, ***B,*** Stenting, ***C,*** Post-stenting. Overexpansion *(arrow)*.

In this study, we investigated the relationship between vessel overexpansion and restenosis in 167 patients undergoing coronary artery stent implantation.

Patients and Methods

Study Design

This prospective, randomized, non-blinded trial was designed to compare 2 stenting strategies in patients with marked size differences between their proximal and distal reference diameters. The Ethics Committee of Union Hospital, Fujian Medical University, approved the study, and all patients provided written informed consent before enrollment.

From January 2009 to December 2010, a total of 653 consecutive adult patients (≥ 18 years old) undergoing PCI at the Cardiology Department of Union Hospital, Fujian Medical University, were analyzed. Among the 653 patients, 184 lesions of 167 patients met the criteria and were included in the study according to quantitative coronary angiography (QCA) results. Inclusion criteria were as follows: (1) *de novo* lesions; (2) lesions in a native coronary artery; (3) 3.50 mm ≥ target vessel diameter ≥ 2.25 mm and a difference between the proximal and distal reference diameters (ΔD) of ≥ 0.25 mm (defined as a "significant" difference in reference diameters); (4) nonostial location of the lesion; (5) 30 mm ≥ lesion length ≥ 12 mm; and (6) successful stent deployment. Exclusion criteria were as follows: (1) bifurcation lesion; (2) severe heart, liver, or kidney dysfunction; (3) blood disease, autoimmune disease, or severe bleeding tendency; (4) severe valvular disease, cardiomyopathy, congenital heart disease, or pericardial disease; (5) cancer or other disease causing a life expectancy < 6 months; (6) patient intolerance to double antiplatelet therapy; (7) coronary artery bypass graft; (8) aneurysmatic coronary artery; (9) chronic total occlusion; and (10) follow-up period of < 1 year.

Stent Strategy

One of 2 stent strategies was chosen for each patient: a single stent, with high-pressure balloon inflation (balloon: artery [B: A] ratio ≥ 1.2) using 9.3±2.8 atm (group A, Figure 1); a single stent, with high-pressure balloon inflation using 9.6±2.6 atm at the proximal segment and low-pressure balloon inflation (B: A ratio < 1.2) using 7.5±1.4 atm at the distal segment (group B, Figure 2), respectively. The size of the stent was based on the average diameter of the proximal and the distal reference vessel. Stent implantation was performed according to standard techniques. A non-compliant balloon was adopted if post-dilation was needed.

Interventional Procedure

Routine PCI through radial artery access or femoral approach was performed with 7/8F or 6/7F guiding catheters, respectively. Either SES (Cypher™, Cordis Corporation) or PES (Taxus™, Boston Scientific) was selected by the operator for all patients. Use of different types of DESs in the same vessel was not allowed.

All patients were administered with 100 mg of aspirin orally, and a loading dose of 300 mg of clopidogrel the day before the procedure or 600 mg immediately before the intervention. During the procedure, heparin (100 U/kg) was administered intravenously. Additional heparin boluses (2000 U each) were given every hour during the procedure to maintain an activated clotting time of 250-300 s. Glycoprotein IIb/IIIa antagonists were not used in this study.

After intracoronary injection of 200 μg of nitroglycerin, at least 2 near-orthogonal angiograms of the target vessel were obtained to ensure that there was no vessel overlap or foreshortening. After assessment of the stenting inclusion and exclusion criteria, each eligible patient was randomly assigned to undergo treatment with strategy A or B.

Angiographic Analysis

Angiographic analyses were performed before and after all interventions and at 12 months. All angiograms were separately analyzed by 2 independent, experienced angiographers. The MLD inside the stent and the reference diameter were calculated to determine restenosis at follow-up. Measurements included the stented area, with measurement from shoulder to shoulder (in-stent), and the total treated area plus 5 mm of that area on either side (in-segment). The proximal and distal reference segments were defined as the most normal-looking segments within 5 mm proximal or distal to the lesion, respectively. Restenosis was defined as a diameter stenosis of ≥50%.

Follow-up and End Points

All patients were prescribed lifelong aspirin (100 mg/d). Clopidogrel (75 mg/d) was given for 12 months after stent implantation. The follow-up period for all patients was 12 months. All end points and adverse events were determined by an independent clinical events committee.

The primary end point was late lumen loss. The secondary end points were the rate of restenosis and the rate of the combined clinical events during the follow-up period, including TLR, stent thrombosis, myocardial infarction, heart failure, and death.

Statistical Analysis

Statistical analysis was performed with SPSS19.0 (SPSS Inc., Chicago, IL, USA). Quantitative data are presented as mean value ± SD. Continuous valuables were compared by one-way analysis of variance. Categorical variables were compared by the chi-square test or Fisher's exact test analysis. Differences with a p-value < 0.05 were considered statistically significant.

Results

Patient Characteristics

Of the 167 patients studied, strategy A was used in 85 patients and strategy B in 82 patients. The interval from PCI to follow-up was 12 months. There were no significant differences in the baseline clinical data among patients undergoing any of the stent strategies (Table I).

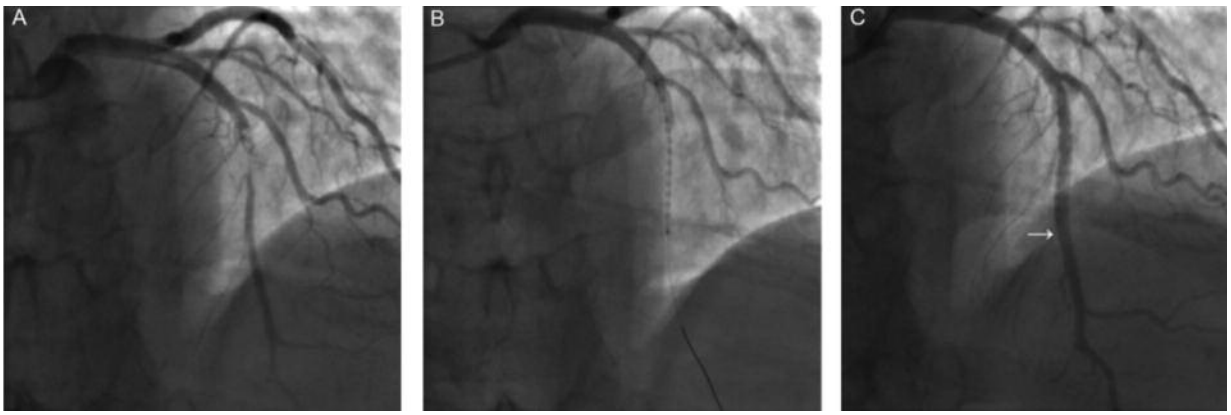

Figure 2. Strategy B: Use of a single stent with high-pressure balloon inflation at the proximal and low-pressure balloon inflation (balloon-to-artery ratio < 1.2) at the distal end. ***A,*** Pre-stenting, ***B,*** Stenting, ***C,*** Post-stenting. Non-overexpansion *(arrow)*.

Table I. General clinical characteristics.

Parameter	Group A (n = 85)	Group B (n = 82)	*p* value
Total ISR patients			
Age (years)	66.9 ± 9.2	66.6 ± 8.5	0.834
Male, n (%)	62 (72.9)	63 (76.8)	0.152
Systemic hypertension, n (%)	63(74.1)	59 (72.0)	0.674
Hypercholesterolemia, n (%)	61 (71.8)	58 (70.7)	0.942
Diabetes mellitus, n (%)	26(30.6)	22 (26.8)	0.823
Smoking history, n (%)	21 (24.7)	19 (23.2)	0.671
Prior myocardial infarction, n (%)	9 (10.5)	7(8.5)	0.334
Clinical presentation			0.652
Acute coronary syndromes, total, n (%)	16 (18.8)	15 (18.3)	
Unstable angina, n (%)	9(10.5)	8 (9.8)	
NSTEMI, n (%)	3 (3.5)	3 (3.7)	
STEMI, n (%)	5 (5.9)	4 (4.9)	

Age is presented as mean ± SD. Other data are presented as number (%). NSTEMI, Non-ST-elevation myocardial infarction: STEMI, ST-elevation myocardial infarction.

Angiographic Characteristics

There were no significant differences among the 2 groups in terms of the target vessel, number of diseased vessels, reference vessel diameter, mean total lesion length, deployment pressure, stent type, or percentage of stenosis (Table II).

Quantitative Coronary Angiography

The post-procedural MLD in group A was significantly larger than those in groups B (2.40 ± 0.18 mm vs. 2.89 ± 0.21 mm, 2.45 ± 0.14 mm vs. 2.49 ± 0.24 mm, respectively, $p < 0.001$). Although stent overexpansion increased the early minimum lumen diameter, it also increased the prevalence of late lumen loss at the distal edge of the stent (A: 18.22 ± 0.56%; B: 5.63 ± 0.41%, $p < 0.001$) (Table III).

Discussion

Given the association of DESs use with late thrombotic risk, an analysis of the stent strategy

Table II. Angiographic findings.

Parameter	Group A (n = 85)	Group B (n = 82)	*p* value
Coronary artery treated			0.688
LAD, n (%)	52 (55.9)	48 (52.7)	
LCX, n (%)	14 (15.1)	11 (12.1)	
RCA, n (%)	27 (29.0)	32 (35.2)	
Reference vessel diameter (mm)			
Proximal	2.96 ± 0.17	2.99 ± 0.14	0.245
Distal	2.40 ± 0.18	2.45 ± 0.14	0.073
ΔD	0.55 ± 0.05	0.54 ± 0.04	0.142
Mean lesion length of total cohort (mm)	20.1 ± 3.31	20.0 ± 3.05	0.715
Preprocedure stenosis (%)	77.5± 4.99	77.3 ± 4.91	0.830
Pressure(atm)			
Proximal	9.3±2.8	9.6±2.6	0.076
Distal		7.5±1.4	
Stent type			0.462
SES	51	45	
PES	42	46	

Diameter and length are presented as means ± SDs. All other data are presented as number (%). LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

used in patients with differently sized distal and proximal reference diameters is particularly important. To our knowledge, this is the first study to compare the 12-month restenosis outcomes among patients treated with 2 different stenting procedures. Stent overexpansion increased the MLD in the early period and resulted in a larger lumen at follow-up. There was no difference in the occurrence of in-stent restenosis (ISR) between the balloon overexpansion and non-overexpansion groups; however, the overexpansion group had an increased tendency towards neointimal proliferation at the distal edge of the stent at 12 months. Late lumen loss was more apparent in the overexpansion group than in the non-overexpansion group.

The use of DESs is associated with decreased rates of restenosis and TLR[6]. However, stent implantation may injure the vascular wall and provide a marked and sustained stimulus for the proliferation of neointima and SMCs[7]. Smooth muscle cells, which serve as the major responder to injury within the vessel wall and can express various adhesion molecules[8], play an important role in the initiation of restenosis. For this reason, DESs have failed to eliminate the appearance of restenosis after stenting[9]. To address this issue, stent overexpansion (i.e., expansion to a greater diameter than suggested by the manufacturer) appears to be a rational approach to achieve a larger lumen. However, this procedure may produce an asymmetric distribution of the stent strut and injure the vascular wall[10].

In the present study, although overexpansion increased the early vascular lumen cross-sectional area, it also markedly increased late lumen loss. The ratio of late lumen loss in the overexpansion group at the 12-month follow-up was 18.22%, compared to 5.63% in the normal expansion group. The late lumen loss was primarily due to neointima hyperplasia and cell proliferation.

The degree of SMC proliferation depends on the degree of arterial injury induced by stenting. Use of a larger B: A ratio increases the likelihood of severe proliferation and restenosis[10,13]. During the procedure, most of the internal elastic lamina may be ruptured by the stent struts, especially under conditions of overexpansion and high balloon pressure, which can result in arterial wall injury[11]. Robert et al[12] used intravascular ultrasound in a porcine coronary artery model to determine the relationship between neointimal hyperplasia and the B: A ratio after bare-metal stent implantation. Although larger B: A ratios resulted in marked neointimal hyperplasia beyond the stent edges, even a B:A ratio of 1.1:1 caused significant neointimal hyperplasia. These outcomes indicate that there is a strong relationship between coronary artery overexpansion and neointimal hyperplasia. Schwartz et al[13], who also implanted coiled stents into a porcine coronary artery model, found that most of the stent struts broke the internal elastic lamina, except for a few struts that simply compressed the underlying medial layer.

Table III. Quantitative angiographic analysis and MACE at follow-up.

Parameter	Group A (n = 85)	Group B (n = 82)	*p* value
Quantitative angiographic analysis			
Ratio of restenosis, total n (%)	11 (12.9)	9 (11.0)	0.112
In-stent	3 (3.5)	4 (4.9)	0.481
In-segment	5 (5.9)	5 (6.1)	0.584
Post-diameter in distal (mm)	2.89 ± 0.21	2.49 ± 0.24	
Follow-up diameter in distal (mm)	2.39 ± 0.12	2.36 ± 0.15	
Percentage of late lumen loss (%)	18.22 ± 0.56	5.63 ± 0.41	<0.001
MACE, n (%)			0.061
Distal dissection	3 (3.2)	0	
Myocardial infarction	0	0	
Stent thrombosis	0	0	
Target-lesion revascularization	7 (8.2)	6 (7.3)	
Heart failure	2 (1.9)	0	
Death	0	0	

Percentage of late lumen loss is presented as a number (%). All other data are presented as means ± SD. "Post" indicates finding after the final procedure.

Their results imply that trauma caused by the overstretched stent leads to SMC proliferation.

Although strategies such as overexpansion, high balloon pressure, and aggressive balloon dilatation are designed to increase the initial luminal diameter while stenting, they may actually lead to substantial vessel wall injury, causing proliferation of the SMCs and intima and resulting in restenosis[14-16]. Moreover, by 6 months after DES implantation, the eluted drug has been completely released. Hypersensitivity reactions mediated by the polymer evoke persistent inflammation and late malposition[17]. In addition to trauma-mediated inflammation, inflammation due to hypersensitivity can also influence the intensity of the neointimal response[18]. Persistent inflammation may induce growth factors, cytokines, and the extracellular matrix to accumulate in the injured vessel wall and cause the proliferation of vascular SMCs[19,20]. Enhanced tissue factor expression (induced by injury and the polymer), as well as persistent endothelial dysfunction and cell hyperplasia, may contribute to the occurrence of ISR[21,22].

It is difficult to evaluate restenosis with the use of DESs. Researchers initially applied late lumen loss as a tool to estimate the outcome of different coronary interventions, such as balloon angioplasty, stenting, and atherectomy[23]. In our study, we used a late lumen loss as a potential method to evaluate restenosis. Although we did not find a relationship between overexpansion and in-stent restenosis, overexpansion was closely related to late lumen loss, especially at the edge of the stent. Although late lumen loss did not reach the statistical degree of restenosis, it could increase the possibility of restenosis in a longer follow-up period.

This study focused on the patterns of the target vessel. Most patients in this study had simple target vessel patterns associated with a favorable outcome. Bifurcation lesions were excluded. Furthermore, we did not use IVUS or OCT to estimate the lumen. If these methods were used, would provide a better results. However, these would not influence the clinical results.

Conclusions

Compared with overexpansion, the use of B:A ratio not ≥ 1.2 might prevent the late lumen loss that is associated with restenosis. This advantage was observed despite the short follow-up period.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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