Over-expansion of second-generation drug-eluting stents, risk of restenosis, and relation to major adverse cardiac events

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DOI: 10.31083/j.rcm.2020.03.27

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1. Introduction

Percutaneous coronary intervention (PCI) is an effective treatment for coronary artery stenosis. Despite that the use of drug-eluting stents (DESs) markedly reduce in-stent restenosis (ISR) and target lesion revascularization (TLR) compared with the use of plane balloon angioplasty and bare-metal stents (Byrne et al., 2017; Nabel and Braunwald, 2012), ISR remains an unsolved issue clinically. Stenting coronary artery injures the stented segment and triggers a series of repair and/or inflammatory mechanisms, leading to proliferation of vascular smooth muscle cells, neointimal hyperplasia, and resultant ISR (Carter et al., 1994; Schwartz et al., 1992). Previous studies showed that with the introduction of the second-generation DESs, ISR was markedly reduced to ≤ 5% of all patients who were subjected to PCI (Pleva et al., 2018) but remained high (up to 15%-20%) in the patient subset receiving suboptimal intervention (Steinvil et al., 2016). Many factors, such as the lesion's or procedural characteristics, contribute to suboptimal intervention results, in which stent expansion conditions frequently influence ISR. Moreover, a major determinant of ISR is the post-procedural minimal lumen diameter (MLD) immediately after PCI (Hoffmann et al., 1998; Kastrati et al., 1997). Research efforts, such as the use of sizable non-compliance balloon with high-pressure post-dilation, have been attempted to improve post-procedural MLD. However, such operation may induce more severe vascular wall injuries due to stent over-expansion, resulting in repair and/or inflammation reaction and likely increase in ISR risk.

Based on the abovementioned hypothesis, in this cohort study, we aimed to examine the impact of stent expansion conditions on the long-term clinical outcomes in patients who received DES implantation.

2. Methods

2.1 Patient selection and study design

This is a prospective cohort study. Patients and lesions with the following criteria were considered eligible: 1) stable angina, unstable angina, or non-ST-segmental elevation myocardial infarction (NSTEMI); 2) de novo significant coronary stenosis treated with the 2nd generation DESs; 3) angiographic success after stenting; and 4) completion of follow-up angiography 12 ± 1 months after index PCI. Angiographic success was defined as a residual di-
ameter stenosis of < 20% with grade 3 TIMI flow. Additionally, severe dissection ≥ type-C at proximal or/and distal stent-end according to NHLBI classification or other requirements for bailout SB stenting was also deemed to be angiographically unsuccessful.

Patients and lesions with following criteria were excluded: 1) ST-segmental elevation myocardial infarction (STEMI) within 4 weeks; 2) post-procedural stent under-expansion; 3) serious renal insufficiency (eGFR < 30 mL/min); 4) obvious hematopoietic disorders (e.g., platelet count < 100 x 10^9/L or > 700 x 10^9/L, leukocyte count < 3 x 10^9/L); 5) intolerance to long-term dual antiplatelet therapy; and 6) life expectancy of < 12 months.

Stent over-expansion was defined as ≥ 1.05 of the stented segment over reference artery diameter (S:A) to reduce the measurement error. S:A ≥ 0.8 and < 1.05 were deemed as norm-expansion (Fig. 1). According to the stent expansion conditions, patients with ≥ 1 over-expanded stented lesions were classified into the over-expansion group. Otherwise, they were classified into the norm-expansion group (Fig. 2).

2.2 Ethics approval and consent to participate

This study is approved by the Ethics Committee of Fujian Medical University Union Hospital (Research project approval ethics number is 2019KY053), and all patients provided written informed consent before enrollment.

2.3 Medication and stenting

All patients received a pretreatment of aspirin and clopidogrel at the loading dose. Intra-procedural heparin (70-100 U/kg) was administered intravenously at the beginning of PCI. Additional heparin boluses (1000 U) were given per hour to maintain an activated clotting time of 250-300 s. Post-procedurally, aspirin was maintained indefinitely, and clopidogrel was maintained for 12 months unless contraindicated. Low molecular weight heparin and platelet glycoprotein receptor antagonists were used at the discretion of the operators.

All stents were the 2nd generation DESs, including Resolute (Medtronic, Minneapolis, Minnesota), Xience V (Abbott Vascular, Santa Clara, California), Firebird2 (Micropor, Shanghai, China), Excel (JW, Shandong, China), and Partner (Lepu, Beijing, China).

Stent size was chosen based on 1.0-1.1 folds of the distal reference vessel diameter. Overlapping stent to cover the whole lesion was allowed.

2.4 Angiography analysis

Coronary angiography was obtained pre- and post-procedurally, and at 1-year follow-up after intracoronary injection of 200 ug nitroglycerin. Quantitative coronary analysis (QCA) was performed in the stented segment (in-stent) and 5 mm proximal or distal to the stented segment (in-segment) to measure the reference vessel diameter (RVD) and minimal lumen diameter (MLD) in two orthogonal angiographic views using an automated contour detection algorithm (AW Workstation 4.3: GE Medical Systems, Milwaukee, WI). Acute lumen gain (ALG) was calculated by post-procedural MLD minus pre-procedural MLD, late lumen loss (LLL) by post-procedural MLD minus follow-up MLD, net lumen gain (NLG) by follow-up MLD minus pre-procedure MLD and diameter stenosis percent (DSP) by (RVD-MLD)/RVD x 100%. Binary restenosis (BRS) was defined as DSP > 50% at follow-up.

2.5 Follow-up

Clinical data were collected during hospital stay and by hospital visit or telephone contact at 1, 3, 6, 9, and 12 months after discharge and annually thereafter. Coronary angiographic follow-up was planned at 12 ± 1 months after the procedure.

2.6 Definition of events and end points

Technical primary endpoint was DSP, BRS, and LLL at 12-month follow-up angiography. The clinical primary endpoint was the major cardiac adverse event (MACE), including cardiac death, myocardial infarction (MI), target vessel/lesion revascularization (TLR/TVR), or stent thrombosis (ST). The secondary endpoint was the individual component of MACE.

MI was defined according to the fourth universal definition of MI (Thygesen et al., 2019). TLR/TVR was target vessel/lesion re-therapy either by PCI or CABG. ST was diagnosed according to the Academic Research Consortium definition (Cutlip et al., 2007).

2.7 Statistical analysis

All analyses were performed with SPSS (version 20.0, Chicago, IL, USA).

Data were expressed as mean ± SD for continuous variables or frequency (%) for discrete or categorical variables. To compare the differences between groups, student t-test was performed for continuous variables. Chi-square or Fisher's exact test was performed for discrete variables. A P-value of < 0.05 was considered statistically significant. Survival curves were constructed by the Kaplan-Meier method. One logistic regression model was used to identify covariates independently associated with the occurrence of stent over-expansion. The variables used in this analysis included lesion length, eccentric, calcified, predilated, maximum stent inflation pressure, and postdilated and maximum postdilated inflation pressure.

3. Results

A total of 161 lesions of 123 eligible patients among 1024 patients who underwent PCI using DESs at our center from January 2012 to September 2012 were enrolled in this cohort. 75 (46.58%) stented lesions were over-expanded, whereas 86 were norm-expanded. 63 patients with ≥ 1 over-expanded stented lesions were classified into the over-expansion group, whereas the remaining 60 patients were classified into the norm-expansion group.

Clinical and procedural data: The baseline clinical characteristics were comparable between the two groups (Table 1). No significant differences were observed in the lesion's features (location, morphology, length, and diameter stenosis), procedural parameters (pre-dilated, post-dilated, and implanted stent number and length) between the groups (Table 2). Stent maximum inflation pressure (OR = 1.22, 95% CI: 1.02 to 1.45, P = 0.032) was an independent predictor of stent over-expansion.

Angiographic results: Quantitative computer analysis (QCA) measurements showed the lack of significant differences in the pre-procedural RVD, MLD, and DSP between the groups. The post-procedural DSP was significantly reduced with similar RVD and MLD in the over-expansion group. However, follow-up DSP at 1-year was markedly increased with reduced MLD in the over-
expansion group. QCA also showed higher LLL (0.54 ± 0.62 mm vs. 0.31 ± 0.55 mm, \( P = 0.014 \)) in-segment in the over-expansion group (Table 3).

**Clinical outcomes:** In the long-term follow-up, cardiac death, MI, and ST were similar between the groups, Cumulative MACE (17.5% vs. 8.3%, \( P = 0.133 \)) tended to be higher in the over-expansion group. TLR/TVR during the 7-year follow-up period (11.1% vs. 3.3%, \( P = 0.098 \)) increased in the over-expansion group (Table 4). The Kaplan-Meier cumulative MACE-free survival had a better trend in terms of statistical differences in the norm-expansion group than in the over-expansion group (log-rank test; \( P = 0.083 \)). The MACE-free rate during the 7-year follow-up period was 82.5% and 91.7% in the over-expansion and norm-expansion groups, respectively (Fig. 3).

### 4. Discussion

To our knowledge, this work was the first monographic study to explore the relationship between stent over-expansion (S:A \( \geq 1.05 \), not the mismatch between nominal stent and final stent sizes discussed by several studies) and clinical outcomes under contemporary coronary technology. It demonstrated that stent over-expansion was associated with the following: 1) high LLL and DSP at 1-year angiographic follow-up; and 2) high cumulative occurrence of MACE due to increased TLR/TVR during the 7-year clinical follow-up period.

Stent norm-expansion is undoubtedly expected to have favorable outcomes, whereas under-expansion leads to unfavorable outcomes whether bare metal stents or DESs were used (Fujii et al., 2005; Nakamura et al., 2016). Numerous previous studies
Fig. 2. Flow chart. The subjects for comparison of angiography follow-up were lesions and subjects for comparison of clinical end points were patients. Abbreviation: PCI, percutaneous coronary intervention.

Fig. 3. Kaplan-Meier curves of time to freedom from MACE showed a worse tendency for statistical differences in the stent over-expansion group, which should be avoid. Abbreviation: MACE: major cardiac adverse event.

showed that immediate residual stenosis of \( \leq 20\% \) was acceptable (Kozuma et al., 2019; Watanabe et al., 2018) and was considered an angiographic success (Smith et al., 2006), because the cut-off point was associated with relatively lower rate of ISR and ST. However, an increasing amount of evidence indicated that post-procedural MLD was a key determinant of ISR (Kuntz et al., 1993).

To increase MLD or diminish residual stenosis, post-dilation has been broadly adopted clinically with sizable (or even over-sized) non-compliance balloons on one hand (Romagnoli et al., 2008), and on the other hand, intravascular ultrasound (IVUS) was used for guidance of stent selection, which tended to choose bigger stents than usual. Hence, stent over-expansion in the real world is not infrequent in the clinic. Here, raises a question whether stent over-expansion is safe and efficacious.

In the BMS era, Peter et al. (Sick et al., 2003) conducted a prospective cohort showing that optimal results regarding ST and ISR were achieved with mild residual stenosis between 0% and 15% after stent implantation, but the restenosis rates reached up to 30% at that time. For DESs, Marco et al. (Costa et al., 2008) cited the concept of geographical miss (GM) to first-generation drug eluting stent era. Longitudinal GM indicates balloon injury or uncover plaque. Axial GM indicates under- or over-expansion (S:A < 0.9 or > 1.3). Lesions with GM characteristics showed twofold to threefold increase in the endpoints of MI and TVR. This result emphasized the importance of optimal stent deployment but low over-expansion count. Several studies encouraged the use of IVUS to guide optimal stent expansion (Russo et al., 2009; Sarno et al., 2011). Intracoronary imaging can value reference vessel diameter and achieve optimal strut apposition and largest luminal area, but no study has focused on S: A. Moreover, the cost and time consumption of this approach hinder its routine use.

In the present study, we found higher LLL and DSP at 1-year
A high rate of stent over-expansion was observed in this study, which can be related to the inclusion of difficult lesions (38.51% type C lesions). Such high rate is also a reminder that stent over-expansion is common in clinical practice. The baseline in this study showed no difference, but the tendency of calcification, stent length, and stent maximum inflation pressure were highly evident in the over-expansion group. Regression analysis also confirmed that stent maximum inflation pressure is an independent predictor of stent over-expansion. High resistance lesion, such as calcium or high plaque burden lesion, can cause a "dogbone" effect. Long lesion occurs along with long taper vessel, and the balloon that is selected based on the middle part of the vessel is oversized for the distal part of the vessel. In such cases, stent over-expansion can be made by inducing high pressure with a semi-compliant balloon, which deserves further attention.

This study had several limitations. First, the nonrandomized single center study nature with a relatively small sample size could limit the confirmatory conclusions. Second, this study included only the patients with 1-year angiographic follow-up data instead of all comers. The potential confounders or selection bias that might affect the outcomes could not be completely ruled out despite that the baseline clinical and procedural characteristics were comparable between the groups. Third, we did not explore the impact of repairing and inflammation responses on the long-term outcomes and we failed to explain the underlying mechanisms.

Table 1. Clinical characteristics

|                        | Over-expansion | P value |
|------------------------|----------------|---------|
| Age (years)            | 62.43 ± 9.53   | 0.794   |
| Female, n (%)          | 8(10.67%)      | 0.22    |
| BMI                    | 24.53 ± 2.70   | 0.735   |
| LVEF (%)               | 63.70 ± 9.86   | 0.265   |
| Hypertension, n (%)    | 47(62.67%)     | 0.987   |
| Diabetes, n (%)        | 17(22.67%)     | 0.55    |
| Hyperlipidemia, n (%)  | 26(34.67%)     | 0.431   |
| Smoker, n (%)          | 35(46.67%)     | 0.446   |
| Family history, n (%)  | 1(1.33%)       | 0.226   |
| Prior MI, n (%)        | 22(29.33%)     | 0.158   |
| Prior PCI, n (%)       | 19(25.33%)     | 0.971   |
| Stable angina, n (%)   | 20(26.67%)     | 0.735   |
| Unstable angina, n (%) | 34(45.33%)     | 0.998   |
| NSTEMI, n (%)          | 21(28.00%)     | 0.729   |
| Aspirin, n (%)         | 73(97.33%)     | 0.763   |
| Clopidogrel, n (%)     | 75(100%)       | -       |
| Statins, n (%)         | 75(100%)       | 0.499   |

Table 2. Angiographic and procedural characteristics

|                        | Over-expansion | P value |
|------------------------|----------------|---------|
| Lesion location, n (%) | Yes (N=75)     | 0.382   |
| LAD                    | 32(42.67%)     | 0.042   |
| RCA                    | 23(30.67%)     | 0.22    |
| LCX                    | 11(14.67%)     | 0.158   |
| LM                     | 9(12.00%)      | 0.035   |
| Angulation ≥ 45°       | 5(6.67%)       | 0.035   |
| Calcified              | 14(18.67%)     | 0.035   |
| Chronic total occlusion| 9(12.00%)      | 0.035   |
| Bifurcation            | 13(17.33%)     | 0.035   |
| Lesion length(mm)      | 22.83 ± 17.05  | 0.035   |
| Pre-dilation, n (%)    | 52(69.33%)     | 0.035   |
| Stent number, n (%)    | 1               | 0.308   |
| 1                      | 51(68.00%)     | 0.035   |
| 2                      | 18(24.00%)     | 0.035   |
| 3                      | 5(6.67%)       | 0.035   |
| 4                      | 1(1.33%)       | 0.035   |
| Stent length (mm)      | 37.24 ± 21.51  | 0.035   |
| Maximal stenting pressure (atm) | 14.68 ± 3.19 | 0.035 |
| Post-dilation, n (%)   | 34(45.33%)     | 0.035   |
| Maximal pressure (atm) | 17.58 ± 4.11   | 0.035   |
| The ratio of stented segment over reference artery diameter (SA) | 1.126±0.837 | 0.035 |
Table 3. QCA measurement

|                  | In-stent |                | In-segment |                |
|------------------|----------|----------------|------------|----------------|
|                  |          | Over-expansion | P value    | Over-expansion | P value    |
| Pre-procedure    |          | Yes (N=75)     | No (N=86)  | Yes (N=75)     | No (N=86)  |
| RVD (mm)         |          | 3.00±0.52      | 2.96±0.48  | 0.773          |
| MLD (mm)         |          | 0.56±0.43      | 0.58±0.39  | 0.652          |
| DSP (%)          |          | 81.39±13.60    | 80.19±12.49| 0.559          |
| Post-procedure   |          | 2.90±0.51      | 2.96±0.54  | 0.49           |
| RVD (mm)         |          | 2.74±0.46      | 2.82±0.50  | 0.856          |
| MLD (mm)         |          | 1.98±4.52      | 4.36±6.46  | 0.009*         |
| DSP (%)          |          | 2.97±0.56      | 2.93±0.52  | 0.587          |
| MLD (mm)         |          | 2.41±0.78      | 2.55±0.58  | 0.174          |
| DSP (%)          |          | 19.03±21.87    | 12.22±15.51| 0.023*         |
| Follow-up at 1-year |      | 2.74±0.46      | 2.82±0.50  | 0.856          |
| RVD (mm)         |          | 1.98±4.52      | 4.36±6.46  | 0.009*         |
| MLD (mm)         |          | 2.97±0.56      | 2.93±0.52  | 0.587          |
| DSP (%)          |          | 2.41±0.78      | 2.55±0.58  | 0.174          |
| MLD (mm)         |          | 19.03±21.87    | 12.22±15.51| 0.023*         |
| Lumen changes    |          | ALG (mm)       | 2.31±0.51  | 2.25±0.56      | 0.406      |
| RVD (mm)         |          | LLL (mm)       | 0.43±0.61  | 0.27±0.48      | 0.065      |
| MLD (mm)         |          | NLG (mm)       | 1.89±0.81  | 1.98±0.62      | 0.428      |
| DSP (%)          |          | 6(8.00%)       | 3(3.5%)    | 0.306          |
| Binary restenosis at 1-year |    | 2(3.2%)       | 0          | 0.496          |

Abbreviations: QCA, quantitative computer analysis; ALG, acute lumen gain; BRS, binary restenosis; DSP, diameter stenosis percentage; LLL, late lumen loss; MLD, minimal lumen diameter; NLG, net lumen gain; RVD, reference vessel diameter; *P < 0.05.

Table 4. Cumulative occurrence of MACE

|                  | Over-expansion group | Norm-expansion group | P value |
|------------------|----------------------|----------------------|---------|
| MACE at 1-year   | 2(3.2%)              | 0                    | 0.496   |
| Death            | 0                    | 0                    |         |
| MI               | 1                    | 0                    |         |
| ST               | 0                    | 0                    |         |
| TVR              | 1                    | 0                    |         |
| MACE at 3.5-year (42months) | 4(6.3%) | 0 | 0.119 |
| Death            | 1                    | 0                    |         |
| MI               | 1                    | 0                    |         |
| ST               | 0                    | 0                    |         |
| TVR              | 2                    | 0                    |         |
| MACE at 7-year   | 11(17.5%)            | 5 (8.3%)             | 0.133   |
| Death            | 5(7.9%)              | 2(3.3%)              | 0.44    |
| MI               | 3(4.8%)              | 2(3.3%)              | 0.688   |
| ST               | 0                    | 0                    |         |
| TVR              | 7(11.1%)             | 2(3.3%)              | 0.098*  |

Abbreviations: MACE, major adverse cardiac events; ST, stent thrombosis; TVR, target vessel revascularization; *P < 0.10.

5. Conclusions

Stent over-expansion is associated with the significant increase in LLL and DSP at 1-year angiographic follow-up and with the increasing trend of cumulative MACE during 7-year clinical follow-up period compared to stent norm-expansion and should be avoided.

Authors' contributors

Yi Tao: data collection and analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval.

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Acknowledgements

This study was supported by the National Natural Science Foundation of China (mainly by Grant No. 81370311, partially by Grant No. 81670332) Scientific and Technological Innovation Project of Fujian Province (No. 2016Y9030). We thank them for support, also all the peer reviewers and editors for their opinions and suggestions.

Conflict of interest

The author declares no conflicts of interests.
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