Branch ostial optimization treatment and optimized provisional t-stenting with polymeric bioresorbable scaffolds

Ex-vivo morphologic and hemodynamic examination

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Abstract
The optimal side-branch (SB) ostium treatment after provisional side-branch scaffolding remains a subject of debate in bioresorbable vascular scaffold (BVS) era. In this study, we evaluated a novel optimized provisional T-stenting technique (OPT) and assessed its feasibility by comparison with T and small protrusion technique (TAP).

Two provisional SB scaffolding techniques (OPT, n = 5; TAP, n = 5) were performed using polymeric BVSs in a bifurcated phantom. The sequential intermediate snuggling balloon dilation, also called ostial optimal technique, was added to OPT but not TAP to dilate the side-branch ostium while the final snuggling balloon dilation applied for both procedures. Microcomputed tomography (microCT) and optical coherence tomography (OCT) were performed to assess morphology, and computational fluid dynamics (CFD) was performed to assess hemodynamics in the scaffolded bifurcations. Compared with TAP in microCT analysis, OPT created shorter neo-carina length than TAP (0.34 ± 0.10 mm vs 1.02 ± 0.26 mm, P < .01), longer valgus struts length (2.49 ± 0.27 mm vs 1.78 ± 0.33 mm, P < .01) with larger MB ostial area (9.46 ± 0.04 mm² vs 8.94 ± 0.09 mm², P < .01). OCT found that OPT significantly decreased the struts mal-apposition (13.20 ± 0.16% vs 1.94 ± 0.54%, P < .01). CFD revealed that OPT generated more favorable flow pattern than TAP, as indicated by less percent (4.68 ± 1.40% vs 8.88 ± 1.21%, P < .01) of low wall shear stress (<0.4 Pa) along the lateral walls.

By using BVSs for bifurcation intervention, the sequential intermediate snuggling balloon dilation is feasible for optimizing ostial SB and facilitating subsequent SB scaffolding. Results show OPT is better than TAP for bifurcated morphology and hemodynamics in this ex-vivo study.

Abbreviations: BCD = bifurcated connecting domain, BVS = bioresorbable vascular scaffold, CFD = computational fluid dynamics, OPT = classic provisional T-stenting, EBC = European bifurcation club, microCT = microcomputed tomography, OCT = optical coherence tomography, OOT = ostial optimization technique, OPT = optimized provisional T-stenting, TAP = T and small protrusion technique. Keywords: bifurcation, bioresorbable vascular scaffold, coronary artery disease, optical coherence tomography, X-ray microtomography

1. Introduction
Percutaneous coronary intervention (PCI) of coronary bifurcation lesions (CBLs) remains challenging. It is associated with a higher rate of major adverse cardiac events than PCI of non-CBLs (13.2% vs 8.0%, P = .009).1 Bioresorbable vascular scaffolds (BVSs) are novel intracoronary therapeutic devices that can be completely absorbed within 2 to 3 years postprocedure. However, systematic evaluation of BVSs in the treatment of CBLs and more secure and effective technological optimizations are still lacking.

In the era of metal drug-eluting stents, simple strategy (1-stent) was the default for the majority of CBLs as most previous studies had not shown additional benefits of complex strategy (2-stent).1–10 Similarly, in the era of BVSs, 1-stent or provisional T-stenting is also preferred for PCI of CBLs, as recommended by the European Bifurcation Club (EBC) because current polymeric BVSs may not be suitable for most 2-stent techniques.1–10

Classic provisional T-stenting (CPT) offers options of 1-stent or 2-stent technique. However, CPT may be associated with incomplete scaffold coverage so there may be a gap in the upper rim of the ostial side-branch (SB) particularly in Y-type CBLs. Although T and small protrusion technique (TAP) greatly eases the SB stent positioning with complete lesion coverage, stent overprotrusion into the proximal main-vessel (PMV) will alter bifurcated morphologies and hemodynamics, increasing the risk...
of thrombosis and restenosis. In the use of BVS, carefully selected patients with simple lesions (e.g., left main lesions, bifurcation lesions with side branch diameters >2 mm diameter, ostial lesions, lesions with moderate, or heavy calcification were excluded) are treated with simple techniques (provisional strategy). It is possible that BVS may increase the incidence of scaffold thrombosis when used in patients with complex diseases, such as bifurcated, defuse, or calcified lesions.[7,9,11,12] Recent studies have shown that polymeric BVS significantly increases scaffold thrombosis by approximately 2 to 3 folds,[13-18] which might be related to the suboptimal implantation technique. Although Abbott has stopped selling Absorb BVS, this is not the end of the bioresorbable platform. Other BRS with different designs (e.g., NeoVas, Firesorb) are now under investigation and have been shown noninferior to CoCr-EES.[19] For this reason, previous stenting techniques should be re-examined in the BVS era, particularly those for the treatment of complex lesion subsets, for instance, CBLs.

Herein, ostial optimization technique (OOT) is proposed as a means of optimizing the SB ostium after stenting the main-branch (MB).[20] In one of our previous studies in which metal stents were used, results suggested that OOT was able to reposition the redundant MB struts over the superior border of the SB ostium (struts ectropion). These results show that 1-stent implantation can have the same effects as 2-stent implantation in rescue SB-stenting. OOT can also facilitate subsequent stent positioning and implantation without causing the struts to protrude into the PMV when the single stenting procedure was converted to a bailout T-stenting or TAP procedure. The latter was called provisional T-stenting with OOT or optimized provisional T-stenting (OPT). It is unclear if the BVS performs better when inserted using the OOT or OPT bifurcation techniques. We simulated 2 different provisional T-stenting procedures with or without OOT in vitro to optimize the technical procedure using BVS.

The goals of the present study are to assess the technical feasibility of OOT in optimizing the SB ostium, and to compare the bifurcated scaffold morphologies and hemodynamics of TAP and OPT with respect to polymeric BVS.

2. Methods

2.1. Experiment protocol

A bifurcation model with a distal bifurcation angle of 60°, made of polyvinyl alcohol based on Murray law (proximal main vessel=0.678 [distal main vessel diameter + side branch diameter]), was adopted for bench testing, which was incubated in a water bath at 37°C.

Two provisional T-stenting techniques (OPT, n = 5; TAP, n = 5) were performed using polymeric BVS (NeoVas, LePu Medical, Beijing, China) to scaffold the MB (3.5 mm BVS) and SB (3.0 mm BVS). A compliance balloon (Apex, Boston Scientific, Maple Grove) was used for pretreating the scaffold side-hole and noncompliance balloon (Quantum Maverick, Boston Scientific, Maple Grove) for postdilation including intermediate/final snuggling balloon dilation and proximal optimization technique (POT). The study was approved by and conformed to the Ethics Committee of Fujian Medical University.

2.2. Scaffolding procedures

The steps in the OPT procedure are as follows (Appendix Figure A, http://links.lww.com/MD/C579):

1. Implanting the PMV-MB scaffold with a slow increase of 2 atmospheres every 5 seconds and up to 10 atmospheres for 30 seconds.
2. POT with a noncompliant balloon at 14 atmospheres to facilitate rewiring of the SB through the most distal cell of the MB scaffold facing the SB ostium.
3. Sequential intermediate snuggling balloon dilation to optimize the ostial SB, which was achieved by first inflating the SB noncompliant balloon at 10 atmospheres and then MB noncompliant balloons at 6 atmospheres for 30 seconds to overturn the redundant struts covering the SB ostium onto the superior border of the ostial SB (OOT).
4. Deploying the rescue scaffold through the open struts into the side branch, and not requiring of strut protrusion into the PMV for complete coverage of the ostial SB as implanting the SB scaffold at 10 atmospheres for 30 seconds.
5. Final snuggling balloon dilation with 2 noncompliance balloons at 8 atmospheres for 30 seconds.
6. Re-POT with a noncompliant balloon at 14 atmospheres for 30 seconds to end the procedure.

The steps in the TAP procedure are as follows (Appendix Figure B, http://links.lww.com/MD/C579):

1. Implanting the PMV-MB scaffold with a slow increase of 2 atmospheres every 5 seconds and up to 10 atmospheres for 30 seconds. POT with a noncompliant balloon at 14 atmospheres to facilitate rewiring of the SB through the most distal cell of the MB scaffold facing the SB ostium. Routine intermediate balloon dilation (non-OOT) by concurrently inflating the SB and MB noncompliant balloons both at 8 atmospheres for 30 seconds to dilate the SB ostium. Implantation of the SB scaffold at 10 atmospheres for 30 seconds with partial strut protrusion into the PMV for complete coverage of ostial SB. Final snuggling balloon dilation with 2 noncompliance balloons at 8 atmospheres for 30 seconds. Re-POT with a noncompliant balloon at 14 atmospheres for 30 seconds to end the procedure.

2.3. MicroCT scanning with raw data acquisition and 3D reconstruction

Each step was observed visually and recorded with a digital recorder (L-1ex/TT02RX, ELMO, Japan) and the final results were acquired by microcomputed tomography (microCT) (Sky-Scan 1176, Kontich, Belgium). The scanning method and settings were: the sample was positioned on a rotary plate with 360° rotation at the speed of 0.367/s, with a total of 800 to 1000 images recorded per sample. The X-ray parameter was set at 65 kV and 385 μA, and scanning with high spatial resolution of 18 μm. After postprocessing, three-dimensional (3D) reconstruction was performed as previously described.[21]

2.4. Morphological analysis

The bifurcated scaffolds were segmented into 4 parts with PMV, MB, SB, and polygon of confluence (POC) (Fig. 1A), and POC and its adjacent segments (3 mm proximal to POC, 3 mm distal to SB and MB ostium) were defined as the bifurcated connecting domain (BCD) (Fig. 1B). MicroCT was used to measure the length (LVS) and angle (AVS) of valgus struts (Fig. 1B) in the stage of SB ostial treatment (OOT/non-OOT) and to assess following parameters in the stage of SB scaffolding (OPT/TAP): the length of neo-carina (LNC), the area of referent (AREF), and minimal (AMIN) scaffold lumen in each segment, the area of the MB
(AMBO) or SB (ASBO) ostium, and the minimal (DMIN) and maximal (DMAX) diameter at the most asymmetric site, which was usually located in the BCD[22–24] (Fig. 1A). Based on the measurements, the index of scaffold lumen symmetry (ISLS) was calculated by DMIN/DMAX, and the percentage of residual in-scaffold stenosis (PRIS) was calculated by 100/C2(AREF/AMIN)/AREF. Here, AMIN may be equal or similar to AMBO or ASBO in most bench testing situations.

Additionally, geometrical distortion of the scaffold struts was analyzed in BCD (Fig. 1B). The ring-to-ring distance (D1) measured along the scaffold long-axis was normalized by the nominated ring-to-ring distance (D0), giving the cell distortion index (D1/D0). The total number of cells (N0) and the cells with D1/D0 ≥ 1.5 (N1) were counted in BCD. The index of scaffold cell distortion was calculated using 100/N0/N1.

2.5. OCT image acquisition and analysis

In this study, 2-dimensional optical coherence tomography (OCT) was performed using the C7-XRTM OCT imaging system with Dragonfly Duo OCT catheter (St. Jude Medical, St. Paul, MN). Automatic pullbacks were performed at 20 mm/s and recorded at 100 frames per second. All images were analyzed by an independent observer using proprietary software. For comparison purposes, malapposition of scaffold struts was calculated in BCD, it was graded by the following criteria: full apposition (no malapposition), incomplete apposition (malapposition > 0 µm), marked malapposition (malapposition > 200 µm), floating struts (malapposition > 500 µm). The rate of severe strut malapposition was expressed as a percentage of the strut footprint with malapposition > 200 µm, as described previously.[25,26]

2.6. Hemodynamic analysis

The modified computational fluid dynamics technique (CFD) was used to assess hemodynamics in the bifurcated scaffold phantoms.[27–29] Briefly, the 3D geometry of the scaffolded bifurcation was established based on microCT-generated raw data rather than virtually simulated data. Bifurcation was then segmented using self-developed code and a commercial software package Solidworks 2015 (Dassault Systemes SolidWorks Corp, Waltham, MA). The fluid domains were subsequently discretized by unstructured tetrahedral/hexahedral mixed cells. Finally, the Navier–Stokes equations for 3D steady flow with rigid wall were solved by commercial CFD code CFX (ANSYS Inc, Canonsburg, PA).

For hemodynamic simulation, blood was assumed to be a viscous incompressible Newtonian fluid with dynamic viscosity 3.5 cP and density 1.06 g/mL.[30] The arteries were presumed to be nonslip rigid walls, and flow velocity at the vessel inlet was presumed to be fixed at 0.5 m/s. The hemodynamic parameters, including the wall shear stress (WSS) and its distribution, the flow velocity, and its streamlines, were assessed in the bifurcated scaffold phantoms, in particular, focused on BCD.
2.7. Statistical analysis
All data analyses were conducted using statistical software packages (SPSS 22.0; SSPS, Chicago, IL). Continuous variables are expressed as mean ± standard deviation and categorical data as counts (%). The Student t test was used for comparison of continuous variables. P < 0.05 was considered statistically significant.

3. Results
The device and procedural success were recorded for all tests in both groups without rupture of scaffolds. Typical examples were shown in Fig. 2 for comparison of OOT versus non-OOT. Figure 3 and Appendix Video A, http://links.lww.com/MD/C580 and B, http://links.lww.com/MD/C581 show comparisons of OPT to TAP morphologically; Fig. 4 shows a comparison of OPT to TAP hemodynamically.

3.1. Bifurcated scaffold morphologies
The morphological measurements are listed in Table 1. OOT created longer LVS than non-OOT (2.49 ± 0.27 vs 1.78 ± 0.33 mm, P < .01) and broader AVS (55.00 ± 4.18 vs 46.20 ± 6.14°, P < .05). Meanwhile, compared with TAP, OPT significantly improved ostial MB morphologies via shorter LNC (0.34 ± 0.10 vs 1.02 ± 0.26 mm, P < .01), larger AMBO (9.46 ± 0.04 vs 8.34 ± 0.09mm², P < .01), lower PRIS (1.02 ± 0.55 vs 13.07 ± 1.09%, P < .01), and higher ISLS (0.91 ± 0.03 vs 0.74 ± 0.06, P < .01) irrespective of similar optimal scaffold expansion along the PMV, MB, and SB, and at SB ostium observed in both treatments. OPT also tended to reduce the severity of scaffold distortion in BCD.

OCT was associated with much less scaffold malapposition in OPT than TAP, as indicated by lower RSMMA in BCD (1.94 ± 0.34 vs 13.20 ± 1.66%, P < .01).

3.2. Bifurcated scaffold hemodynamics
Hemodynamic measurements are listed in Table 2. OPT generated better hemodynamic results than TAP: smaller area (14.41 ± 4.51 vs 26.60 ± 5.02 mm², P < .01) with lower area percentage (4.68 ± 1.40 vs 8.88 ± 1.21%, P < .01) of low WSS (defined by < 0.4 Pa) on branch lateral walls and higher magnitude of mean WSS on the scaffold luminal surface (1.53 ± 0.12 vs 1.26 ± 0.04 Pa, P < .01).

Qualitative analysis showed more favorable flow patterns produced by OPT, as shown in Fig. 4. TAP was associated with significantly lower PMV/MB flow velocity than OPT. The blood flow was also disturbed by creating microturbulence that distributed the area near the neo-carina, particularly on its MB side, suggesting that the protrusion of SB scaffold into POC inherent to TAP is the principal cause of disturbed flow patterns.

4. Discussion
BVSs offers an opportunity but also poses a challenge for PCI of CBLs because BVSs differ from the conventional metal stent platforms in many ways, such as the thicker struts and more fragile structure of the currently available BVS (PLLA-BVS). In this way, the previous stenting techniques and associated procedural steps developed for metal stent platforms should be re-examined until they can be safely used with BVS.

Figure 2. Morphological differences among SB ostia treated with OOT and non-OOT. Photos and microCT-reconstructed 3D images of bifurcated scaffolds showing OOT (upper panels A, B, C, D) to be more effective than non-OOT (lower panels E, F, G, H) with respect to overturning the redundant MB struts covering the SB ostium onto the superior border of ostial SB, resulting in ectropion in more struts, as shown in photos (A vs E, arrow), full 3D images (B vs F), and electronic haft-cut 3D images on the coronal plane (C vs G, solid line). In this particular case, ectropion of the struts could be created completely by OOT but only partially by non-OOT, as indicated by greater length and broader angle of the valgus strut in strut sectional images on the midline coronal plane (D vs H, arrow). 3D = three-dimensional, microCT = micro-computed tomography, OOT = ostial optimization technique, SB = side-branch.
This is the first study to examine the feasibility of OOT in the optimization of the SB ostium and subsequent SB scaffolding. We also to compare the performance of OPT and TAP in bifurcation scaffolding with BVS. Our major findings were as follows: OOT overturn the redundant struts covering the SB ostium onto the superior border of the ostial SB without rupturing the MB scaffold, resulting in lip-like strut ectropion. OOT facilitated subsequent SB scaffold positioning and implantation without excessive protrusion of the rescue SB scaffold after T or T-stenting and small protrusion (TAP), resulting in seamless connection between the MB and SB scaffolds; OPT outperformed TAP in terms of bifurcated morphologies and hemodynamics.

4.1. Proper ways to accomplish OOT

Final single or kissing balloon dilation, once a standard step in enlargement of the side-hole of the MB stent in the treatment of CBLs with 1-stent approach was expected to optimize the SB ostium regardless of debate about its efficacy in reducing ostial SB restenosis or MACE. Likewise, intermediate single or kissing balloon dilation was used to dilate the stent side-hole as well, mainly to facilitate subsequent stent passage when using CPT. OOT differs from intermediate, final, single, and kissing balloon dilation in the following ways: it is a snuggling or mini-kissing balloon dilation technique rather than a standard technique; it was achieved by sequential intermediate snuggling balloon instead of routine intermediate balloon dilation, which were themselves achieved by first inflating the SB with higher pressure (10 atmospheres) followed by MB inflation of the noncompliant balloon at low pressure (6 atmospheres) for 30 seconds as using BVS; sequential intermediate snuggling balloon generated the resultant force better aligned to the natural SB axis, thereby producing better results, specifically a lip-like strut ectropion. In the present study, which was performed with BVS, OOT was associated with longer and more widely angled strut ectropion than routine intermediate balloon dilation, resulting in 2-stent effects with 1-stent implantation and pronounced facilitation of subsequent SB scaffolding as the rescue SB stenting was indicated.

4.2. Differences in performance between OPT and TAP

Even though TAP simplifies the SB scaffold positioning process significantly with complete lesion coverage with respect to rescue SB stenting, stent over-protrusion into the PMV will alter bifurcated morphologies and hemodynamics, which may become more severe with BVS due to its physical properties. OCT is accepted as a gold standard technique for the optimization of BVS implantation. Due to its high resolution, OCT is useful to visualize and evaluate the scaffold struts in vivo. In addition, 3D OCT reconstruction is feasible to evaluate the ostium of SB jailed with BVS and guide selection of proper distal
cell for SB rewiring in provisional bifurcation stenting. Accordingly, systematic imaging assessment using OCT is essential to ensure optimal outcomes with BVS in clinical practice. CFD analysis is another invaluable method for the quantification of scaffold hemodynamics. Previous studies have demonstrated that low WSS (<0.4 Pa) tends to be present in regions with erosion and plaques formation. As shown in the present study, OPT was associated with much better bifurcated scaffold morphologies and hemodynamics than TAP, as clearly evidenced by the larger MB ostial area, shorter neocarina length, and greater luminal symmetry relative to microCT, less severe strut malopposition relative to OCT, smaller low WSS area on branches lateral walls, and less pronounced microturbulence near the neocarina by CFD.

4.3. Clinical relevance of OOT and OPT
Because BVS increases the risk of thrombosis, simpler approaches (1-scaffold or provisional T-stenting) remain the preferred treatments for most CBLs recommended by EBC consensus. However, when using simpler approaches thicker scaffold across the ostial SB may more readily compromise the ostium, leading to acute occlusion and residual stenosis or to chronic strut occlusion and restenosis. There is no consensus on the treatment of struts crossing over the SB ostium. Single balloon or mini-kissing/snuggling balloon dilation has been suggested as more cautious means of expanding the scaffold side-hole at low pressure, but they cannot completely avoid destroying the scaffold structure. OOT with the unique sequential intermediate snuggling balloon technique could prevent distortion or rupture of the struts. More importantly, it creates a lip-like strut ectropion to cover the upper rim of the ostial SB, resulting in 2-scaffold effects with 1-scaffold implantation or avoidance of rescue SB stenting. Moreover, if rescue SB stenting is required, such as in cases of severely compromised SB, dissection, flow impairment, or any combination of these, OPT can easily produce a seamless connection between the SB and MB scaffolds, thereby reducing the risks of scaffold thrombosis.

BVS are considered the fourth revolution in the field of interventional cardiology and are emerging as a promising treatment for patients undergoing primary PCI. However, scrupulous lesion selection, appropriate implantation technique, and the application for systematic intravascular imaging assessment are crucial to achieving better long-term clinical outcome with the currently available devices. For complex CBLs, as 2-scaffold strategy is indicated, only T-stenting is recommended by EBC consensus with avoiding complex techniques such as crush or culotte. However, classical T-scaffolding may bring in the issue of leaving an uncovered gap in ostial SB. This issue can be addressed with post-treatment of final sequential intermediate snuggling balloon (OOT) which, meanwhile, can effectively decrease the need of rescue SB scaffold.

4.4. Study limitations
Despite controlling the procedural cofounders that may affect the results, there are some limitations in our study. First, the model represents an idealized bifurcation without lesions, whereas CBLs...
in real clinical settings are usually much more complicated, and the resultant scaffold morphology may be affected by the specific characteristics of the lesion or the patient’s anatomy. Second, current CFD simulation was based on a steady flow model; while pulsatile flow might form more complex flow patterns. Third, the arteries were assumed to be non-slip rigid walls and the fluid properties to be typical coronary circulatory conditions for CFD simulations, which may not really reflect the clinical scenarios. Thus, further studies are warranted to confirm our observations.

5. Conclusions

In conclusion, when using polymeric BVs for treatment of CBLs, OPT is technologically feasible for optimizing the SB ostium and facilitating the implantation of subsequent SB scaffolding; as required rescue SB scaffolding, OPT is associated with better bifurcated morphologies and hemodynamics than TAP, and such benefits may translate into improved clinical outcomes but further clinical validation is necessary.

Author contributions

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