Original Article

Evaluation of a tapered polymer-free sirolimus-eluting stent in porcine coronary arteries

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Received September 21, 2015; Accepted January 16, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Background: No stent is yet available for tapering coronary arteries. The purpose of the present study is to evaluate the applicability, efficacy and safety of a novel tapered, polymer-free sirolimus eluting stent (t-PFSES) specifically designed for tapering coronary arteries. Methods: 28 pigs underwent the placement of 56 oversized stents (control, n = 28, t-PFSES, n = 28), and quantitative coronary angiography (QCA) and histopathologic analysis were performed at 1, 3 and 6 months follow-up. Results: In proximal segments, both the t-PFSES and control stents lead to similar results, while, in distal segments, the t-PFSES stent was associated with significantly improved angiographic outcomes. Compared with the control stents, t-PFSES exhibited a greater inhibition of neointimal hyperplasia in all stented segments, but the magnitude of the neointimal area was lower in the proximal segments than in the distal segments, (1.15 vs. 1.48 mm², 0.33 vs. 0.8 mm², 0.3 vs. 1.14 mm² at 1, 3 and 6 months, respectively, P > 0.05). Complete re-endothelialization was observed with both stents at 1 month post-procedure, but the t-PFSES stented distal segments had numerically lower inflammation scores (P = NS). Conclusion: The t-PFSES stent is applicable to coronary artery segments with marked tapering (10% tapering or 0.45 mm). Compared with the conventional bare metal stent, t-PFSES appeared to be safer and lead to superior angiographic outcomes, especially in the distal segments of tapering coronary arteries.

Keywords: Polymer-free, drug eluting stent, porcine coronary model, tapered stent

Introduction

Natural tapering of coronary arteries from larger proximal to smaller distal diameters represents a major technical challenge for optimal balloon and stent sizing. For example, the tapering of left anterior descend (LAD) coronary arteries range from 18.14% to 29.9% [1]. Moreover, IVUS studies have revealed that up to 89% of arteries had significant tapering [2-4], averaging 0.22 mm for every 10 mm [2]. As the diameter of currently available stents is uniform along their entire length, interventional cardiologists often face a dilemma when deciding which stent size would yield optimal angiographic results, especially when vessel tapering is > 10%. Determining stent size based on the proximal reference diameter may result in an increased risk of dissection whereas, when based on the distal reference diameter, it may result in suboptimal deployment with an increased risk of stent thrombosis and restenosis.

In pre-stent era, decremental diameter (tapered) balloons have been developed, and found to be safe and effective for the treatment of lesions in coronary arteries with marked segmental tapering [3, 4]. Based on these observations, mechanical modeling studies were conducted to assess the applicability of compliant stents in tapered arteries [5]. It was concluded that compliant stents could be used perhaps even to the exclusion of tapered stents when the rate of decrement in diameter over the length of the stented segment was about 10%.

We developed a decremental diameter (tapered) stent for use in arterial segments with marked tapering. Theoretically, a stent that tapers along with the artery would lead to improved angiographic results as compared to a conventional stent. The present study assessed the applicability, efficacy and safety of such a stent.

Methods

Experimental studies

316L stainless steel balloon expandable tubular stents with a tapered design and nano-
Evaluation of t-PFSES stent in porcine models

porous drug reservoir coated with a 2.2 µg/mm² of rapamycin (Lepu Medical Technology, Beijing) [6]. Drug elution is > 67% complete after 7 days, > 90% complete after 14 days, 100% complete after 28 days. Stent diameters (proximal to distal) used included 3.5→2.5 mm, 3.0→2.5 mm and 3.0→2.0 mm, and the length was 15 mm. 316L Stainless steel bare metal stents served as controls. All stents were individually packaged, coded with a serial number on the packaging label and ETO sterilized. The identity of each serial number was only known to the sponsor to ensure the deployment and analysis of the results in a blinded fashion.

All experimental studies were conducted after approval by the Institutional Animal Care and Use Committee in accordance with Peking University Health Science Department and China Heart Association Guidelines for animal research. Twenty eight Chinese mini-pigs of either sex (23 to 39 kg) underwent stent placement (stent to artery ratio 1.1-1.3:1) in the left anterior descending, circumflex or right coronary arteries (control = 28, t-PFSES n = 28). Three days prior to the procedure, all animals received 300 mg aspirin/day and 75 mg clopidogrel 75 mg/day. Afterwards, they were returned to the care facilities to recover, were fed a normal diet, and received 100 mg aspirin/day for the duration of the study and 75 mg clopidogrel/day for 3 months. At 30 days (n = 10), 90 days (n = 9) and 180 days (n = 9), the animals were euthanized after the follow-up coronary angiography and the stented segments were processed for histological analysis.

Quantitative coronary angiography

Angiographic images of stent implants (n = 56) were saved on a CD-ROM disk in a standard DICOM format and analyzed using a quantitative coronary angiographic analysis software program (INOV A 2100 GE company America). The guiding catheter served as a reference for the calibration for all measurements and the proximal and distal baseline reference vessel diameters, follow-up reference vessel diameters, balloon inflated diameters, post-stent lumen diameters, follow-up lumen diameters and follow-up percent diameter stenosis. The balloon to artery ratio was calculated as the balloon inflated diameter/baseline reference vessel diameter. The percent diameter stenosis was calculated as \[1 - \frac{\text{post-stent reference vessel diameter}}{\text{follow-up lumen diameter}}\] × 100%.

Pathologic evaluation

Immediately following euthanasia, the hearts were harvested and the coronary arteries were perfusion-fixed with 10% buffered formalin at 100 mmHg. The stented coronary artery segments were processed for plastic embedding, staining and morphometric analysis of three sections from the proximal through the distal margin of the stent [7-9]. All specimens were embedded in methyl-methacrylate, sections were obtained with a Beuhler isomet saw (Beuhler, Evanston, IL), polished, mounted on a glass slide and stained with metachromatic stain. All histopathologic analyses were performed by an independent investigator (H.W.J) who was blinded to treatment groups. Vessel morphometry (LEICA Qwin Plus V3.2.1 Software, LEICA, DM LB2 DFC300FX) and morphologic analysis of injury, inflammation and endothelialization were performed according to published methods [7-9]. Stent endothelialization score was defined as the extent of the circumference of the arterial lumen covered by endothelial cells and graded from 1 to 3 (1 = 25%, 2 = 25% to 75%, 3 = > 75%). The injury score was determined according to the method of Schwartz et al. [8], and the average score for each segment was calculated by dividing the sum of the injury scores by the total number of struts on the examined section. Inflammation was graded as 0 = no inflammatory cells, 1 = scattered inflammatory cells, 2 = inflammatory cells encompassing 50% of a strut in at least 25%–50% of the circumference of the artery and 3 = inflammatory cells surrounding a strut in at least 25% to 50% of the circumference of the artery [9].

Statistical analysis

For continuous variables of normal distribution, such as morphometric and morphologic parameters, they were expressed as mean ± SD unless otherwise stated. The mean differences between treatment groups were tested with Student t test, and a P value < 0.05 was considered statistically significant. All statistical anal-
Evaluation of t-PFSES stent in porcine models

yses were performed using SPSS system software.

Results

A total of 56 stents were successfully implanted in the coronary arteries of 28 pigs. All animals survived the intended study interval without clinical complications or angiographic stent thrombosis, and stent migration and fragmentation were not observed either during the procedure or at follow-up. The magnitude of tapering [(proximal vessel diameter - distal vessel diameter)/proximal vessel diameter] in the target vessel segment over a 20 mm length was 18.1±5.7% vs. 18.0±6.2% for t-PFSES and control stents, respectively (P = 0.96).

Quantitative coronary angiography

The baseline vessel diameters in the proximal segments were similar between the t-PFSES and control stents (range 2.10-3.25 mm) as were the balloon to artery ratios (approximately 1.17 to 1, range 1.06-1.31 to 1). The in-stent % stenosis at 30, 90 and 180 days tended to be greater for the t-PFSES group, but without statistical significance (t-PFSES: 10.81±10.73%, 9.00±6.82% and 17.37±1.16%; control: 16.26±10.59%, 15.35±11.12% and 17.32±9.49%, respectively). Both stent types exhibited minimal and similar angiographic narrowing. In distal segments, the balloon to artery ratio differed between groups at approximately 1.09 to 1 and 1.24 to 1 for the t-PFSES and control groups, respectively. Thirty days post-implantation, the t-PFSES group had significantly less in-stent % stenosis (10.98±11.37%) compared with the control stents (23.13±13.68%, P = 0.045) while, at 90 and 180 days, the control (90 days: 25.28±6.69%; 180 days: 23.78±9.94%) and t-PFSES (90 days: 15.91±6.84%; 180 days: 20.66±10.31%) stents exhibited minimal and similar angiographic narrowing (Figure 1). Compared with the control stents, animals treated with the t-PFSES stents tended to yield more benefits in the distal segments. No case of diameter stenosis > 50% were observed for either stent at 30, 90 or 180 days.

Table 1. Histomorphometry findings

<table>
<thead>
<tr>
<th>Histomorphometric findings</th>
<th>Proximal-Control</th>
<th>Proximal-t-PFSES</th>
<th>P* value</th>
<th>Distal-Control</th>
<th>Distal-t-PFSES</th>
<th>P# value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days N = 8 LA (mm²)</td>
<td>2.34±1.36</td>
<td>2.93±0.60</td>
<td>0.273</td>
<td>2.00±1.20</td>
<td>2.72±1.07</td>
<td>0.225</td>
</tr>
<tr>
<td></td>
<td>3.05±1.48</td>
<td>1.90±0.77</td>
<td>0.070</td>
<td>3.34±1.66</td>
<td>1.86±1.23</td>
<td>0.062</td>
</tr>
<tr>
<td>90 days N = 8 LA (mm²)</td>
<td>3.29±1.25</td>
<td>3.10±1.26</td>
<td>0.765</td>
<td>2.84±1.51</td>
<td>2.79±1.61</td>
<td>0.953</td>
</tr>
<tr>
<td></td>
<td>2.24±1.25</td>
<td>1.91±0.96</td>
<td>0.570</td>
<td>2.48±1.26</td>
<td>1.68±0.90</td>
<td>0.164</td>
</tr>
<tr>
<td>180 days N = 8 LA (mm²)</td>
<td>2.29±0.72</td>
<td>2.20±1.58</td>
<td>0.916</td>
<td>2.22±1.91</td>
<td>2.16±1.06</td>
<td>0.957</td>
</tr>
<tr>
<td></td>
<td>2.90±1.50</td>
<td>2.60±1.50</td>
<td>0.668</td>
<td>3.61±2.00</td>
<td>2.47±1.64</td>
<td>0.203</td>
</tr>
</tbody>
</table>

LA = lumen area, nIA = neointimal area. P* value = proximal-Control versus proximal-t-PFSES. P# value = distal-Control versus distal t-PFSES.

Figure 1. In-stent % stenosis in control and t-PFSES stents at 30 (A), 90 (B) and 180 (C) days.
As well, qualitative analysis of angiograms did not identify intraluminal filling defects, edge effects or aneurysms in either group.

Histology

The histomorphometry and a semi-quantitative scoring for injury and inflammation at 30, 90 and 180 days for both the control and t-PFSES stents are summarized in Tables 1 and 2 and Figures 2-9.

After 30, 90 and 180 days, a reduction in the neointimal area in the proximal segments was observed with the t-PFSES stents albeit not significant when compared with the control stents (Tables 1 and 2; Figures 2-9), and resulted in larger cross-sectional lumen area. The mean injury and inflammation scores for the control stents were higher while they were similar all along the stented segments for t-PFSES stents, which translated greater.

At 30, 90 and 180 days, a reduction in the neointimal area was also observed with t-PFSES stents in distal segments (Tables 1 and 2; Figures 2-9). When compared with the proximal segments, the mean injury and inflammation scores for the control stents were higher while they were similar all along the stented segments for t-PFSES stents, which translated greater.

Discussion

Results of the present study revealed that the magnitude of tapering in the target vessel was
Evaluation of t-PFSES stent in porcine models

18.1±5.7% and 18.0±6.2% over 20 mm length for the t-PFSES and control stents, respectively.

To our knowledge, stenting of vessel segments with such a magnitude of tapering has never been demonstrated in either animal or clinical studies, as they are usually excluded [10]. Nevertheless, Timmins et al. have suggested the applicability of compliant stents in arteries with 10% tapering in a real world patient population [5]. Although their results have yet to be proven in randomized controlled trials, many interventional cardiologists believe it is appropriate to dilate the proximal segment post stenting in target lesions presenting with such a small degree of tapering. However, in patients without atherosclerosis, the coronary arteries taper to the greatest degree in the LAD (14-29.9% for each segment) [1]. In previous studies of tapered arteries, the magnitude of tapering in the target vessel segment was greater than 10% [2-4]. In present study, when control stents were deployed in the target lesions, inappropriate larger stent to artery ratios were observed in the distal seg-
The first generation drug-eluting stents revolutionized contemporary percutaneous coronary intervention by reducing in-stent restenosis from 31.7% with bare-metal stents to 10.5% [11]. However, it raised the issue of "late catch up" [15-17] and a higher rate of late stent thrombosis [12-14]. In numerous studies, it was that the long-term presence of stent polymers caused persistent inflammatory reaction and neointimal area as opposed to t-PFSES stents which demonstrated a consistent stent to artery ratio, injury scores and neointima area along the stented segments. We have therefore documented the applicability and superiority of the t-PFSES stents in arteries with approximately an 18% degree of tapering (Figure 10). Until it has been proven by large-scale clinical trials, based on the present results, we suggest to avoid the use of conventional column stents for treating lesions with a marked degree of tapering. We are planning a follow-up study to confirm the applicability, efficacy and superiority of t-PFSES stents in the near future.

Previous studies have established that neointimal proliferation post stenting was proportional to injury [8, 29, 30]. Kornowski et al. found that the degree of arterial injury was also strongly correlated with the extent of the inflammatory reaction, and both injury and inflammation were positively correlated with neointimal proliferation [28]. Because porcine coronary arteries are very similar to those of humans, swines have become a standard experimental model for the study of coronary stents in the preclinical setting. In present study, a greater neointimal area was observed in the distal segments of the conventional columned control stent. This was due, at least in part, to the more extensive injury, which would likely be minimized with the use of a tapered stent. In real
world practice, marked tapering can be observed in the reference vessel of culprit lesions, in long lesions in the LAD, lesions in a bifurcation or anastomosis of a saphenous vein graft and in total coronary occlusion [4]. For tapered lesions, the use of conventional stents may lead to suboptimal angiographic results and poorer outcomes.

As to state above, long lesions located in the LAD often present with significant tapering and the greatest difference between the diameters of the proximal and the distal segments [1-3]. In addition, long lesions are considered a risk factor for restenosis, stent thrombosis and major adverse cardiovascular events [31-33]. To assess the long-term safety and efficacy of the paclitaxel eluting TAXUS stent for the treatment of long, complex coronary artery lesions, Grube et al. randomized 446 patients to either a TAXUS Express stent or an uncoated bare metal stent [34]. At 5-year follow-up, the overall rates of major adverse cardiovascular events, target vessel revascularization, target lesion revascularization and stent thrombosis for the control TAXUS stents were 27.8% vs. 31.3%, 23.7% vs. 22.2%, 21.4% vs. 14.6% and 0.9% vs. 0.9%, respectively. In addition, IVUS investigation revealed high rates of incomplete stent apposition immediately post procedure (control: 6% vs. TAXUS: 13.6%) and at follow-up (control: 5.5% vs. TAXUS: 25.9%). Compared with previous studies for on-label indications [35-37], these results were significantly poorer and likely due to a mismatch between the artery and the stent [1-3]. However, because the magnitude of vessel tapering was not evaluated, it is unknown if the use of a tapered stent would have yielded better results. Lesions located in a bifurcation or anastomosis of a saphenous vein graft, and total coronary occlusion are also risk factors for poor procedural success and high rates of major adverse cardiovascular events, revascularization procedures and stent thrombosis [38-40]. However, none of these trials have evaluated if vessel tapering was present in these complex lesions. Based on the results of the present study, t-PFSES with a tapered design is associated with superior angiographic outcomes than those observed with a conventional stent. This was true for the entire length of the lesion and, especially in the distal segment. For complex lesions such as those mentioned above which might present with marked tapering, one can speculate that a stent with a tapered design would lead to greater benefits.

Study limitations

The present study should set up another control group, a polymer-free sirolimus eluting stent without the tapering design. Moreover, the number of animals for the experiment is somewhat limited.

Conclusion

Use of the t-PFSES is feasible in coronary segments with marked tapering. Compared with a conventional stent, t-PFSES is safer and lead to better angiographic outcomes, especially in the...
distal segment of the culprit lesion. The efficacy and safety of this stent, which is specifically designed for tapering arteries, has to be confirmed in large scale clinical studies.

Acknowledgements

This study was sponsored by Lepu Medical Technology.

Disclosure of conflict of interest

None.

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Evaluation of t-PFSES stent in porcine models


