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Original Article

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

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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 mm^2, 0.33 vs. 0.8 mm^2, 0.3 vs. 1.14 mm^2 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 descends (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-

porous drug reservoir coated with a 2.2 ug/mm^2 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 (INOVA 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-(follow-up lumen diameter/post-stent reference vessel 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-

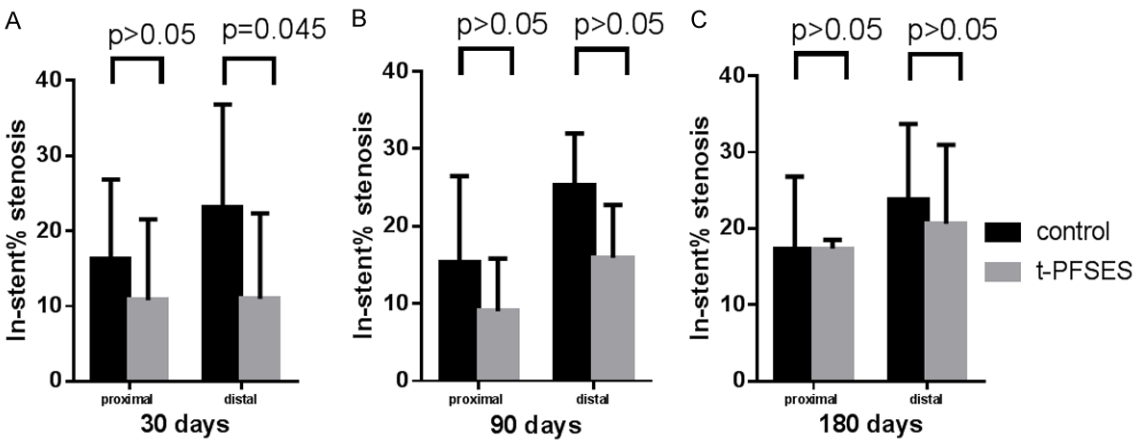

Figure 1. In-stent % stenosis in control and t-PFSES stents at 30 (A), 90 (B) and 180 (C) days.

Table 1. Histomorphometry findings

Histomorphometric findings		Proximal-Control	Proximal-t-PFSES	P^* value	Distal-Control	Distal-t-PFSES	$P^\#$ value
30 days N = 8	LA (mm^2)	2.34±1.36	2.93±0.60	0.273	2.00±1.20	2.72±1.07	0.225
	nIA (mm^2)	3.05±1.48	1.90±0.77	0.070	3.34±1.66	1.86±1.23	0.062
90 days N = 8	LA (mm^2)	3.29±1.25	3.10±1.26	0.765	2.84±1.51	2.79±1.61	0.953
	nIA (mm^2)	2.24±1.25	1.91±0.96	0.570	2.48±1.26	1.68±0.90	0.164
180 days N = 8	LA (mm^2)	2.20±1.58	2.29±0.72	0.916	2.22±1.91	2.16±1.06	0.957
	nIA (mm^2)	2.90±1.50	2.60±1.50	0.668	3.61±2.00	2.47±1.64	0.203

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

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 2. Pathologic scores

Pathologic score		Proximal-Control	Proximal-t-PFSES	P^* value	Distal-Control	Distal-t-PFSES	$P^\#$ value
30 days N = 8	Injury	1.50±1.41	1.25±1.16	0.70	1.88±1.25	0.88±0.99	0.10
	Inflammation	1.50±0.53	1.38±0.52	0.64	1.63±0.52	1.25±0.46	0.14
90 days N = 8	Injury	1.25±1.16	1.13±1.25	0.84	1.50±1.41	1.00±1.00	0.39
	Inflammation	1.88±0.35	1.88±0.35	0.12	2.00±0.00	1.50±0.53	0.55
180 days N = 8	Injury	2.11±1.17	2.10±1.26	1.00	1.89±0.93	1.56±1.13	0.50
	Inflammation	1.89±0.33	1.89±0.33	1.00	1.89±0.71	1.78±0.44	0.72

P^* value = proximal-Control versus proximal-t-PFSES. $P^\#$ value = distal-Control versus distal t-PFSES.

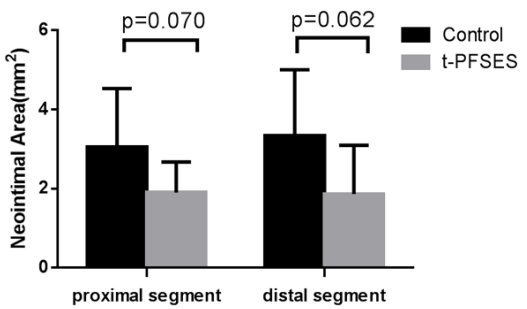

Figure 2. 1 month neointimal area (mm²).

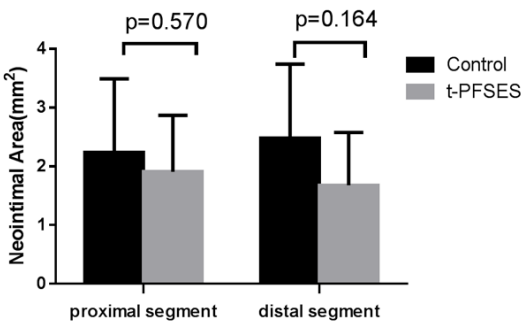

Figure 3. 3 month neointimal area (mm²).

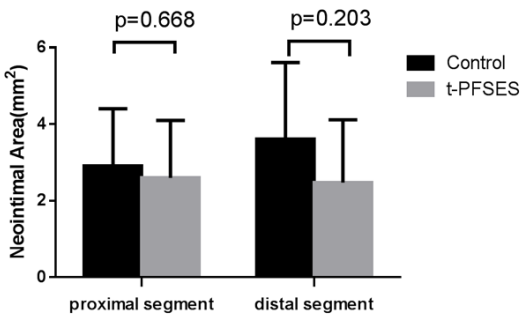

Figure 4. 6 month neointimal area (mm²).

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 were similar between groups, and both stents were consistently associated with a low inflammatory reaction throughout the study. As demonstrated in previous studies, t-PFSES stents inhibited intimal proliferation with the least inflammatory reaction as compared with polymer-based drug-eluting stent.

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.

After 30, 90 and 180 days, the endothelialization scores were similar between stents and showed complete re-endothlialization. The media appeared intact with localized regions of compression in areas of strut-induced vessel injury. Medial necrosis was not observed in any segments.

Discussion

Results of the present study revealed that the magnitude of tapering in the target vessel was

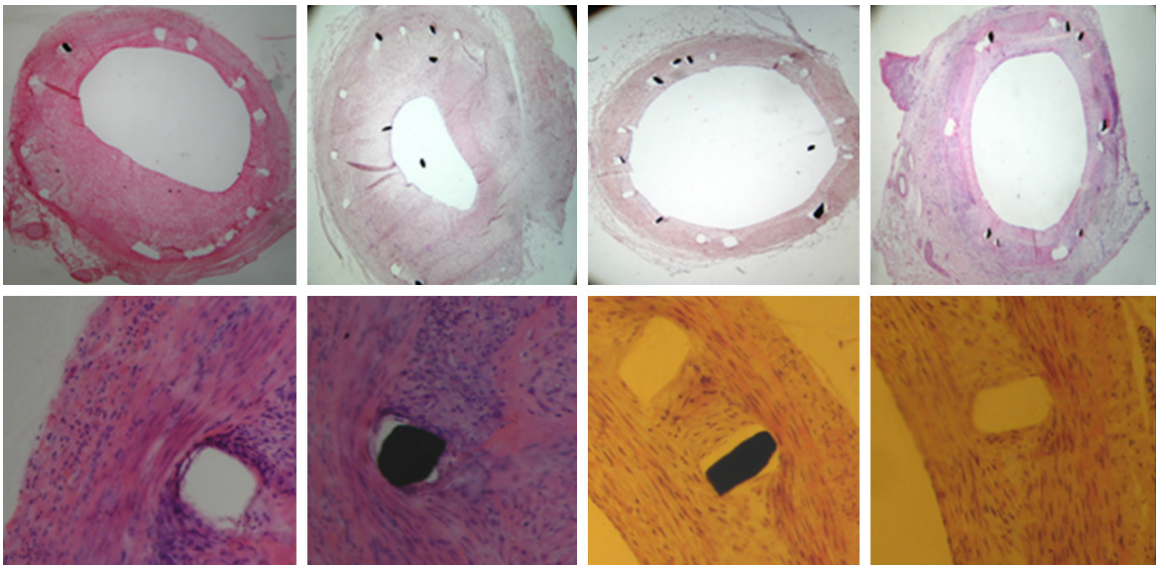

Figure 5. 30-day histopathological photomicrographs (upper panel: 25×, lower panel: 200×) of stented coronary and neointimal areas in the different groups. Control stents proximal; Control stents distal; t-PFSES stent proximal; t-PFSES stent distal.

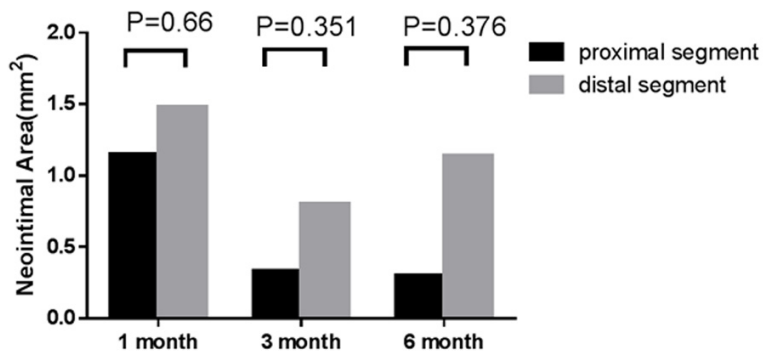

Figure 6. Benefits of the t-PFSES stents gain from the control stents with respect to the neointimal area (mm^2) (neointimal area of control stents minus the t-PFSES stents).

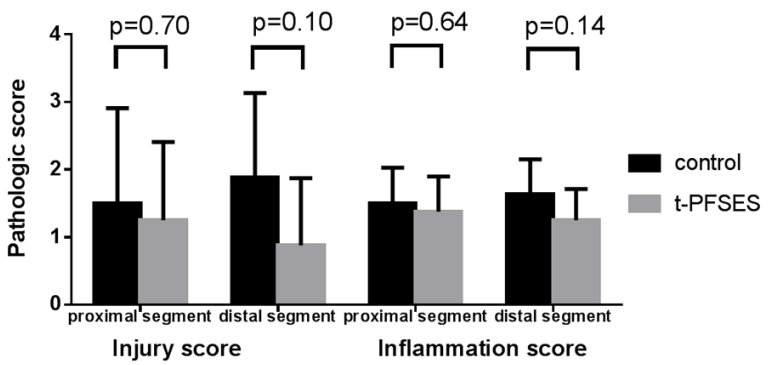

Figure 7. 1 month pathologic score.

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 taperied arteries, the magnitude of tapering in the target vessel segment was gretare 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-

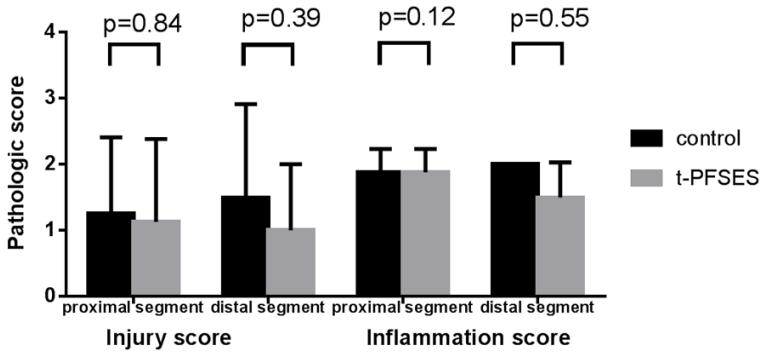

Figure 8. 3 month pathologic score.

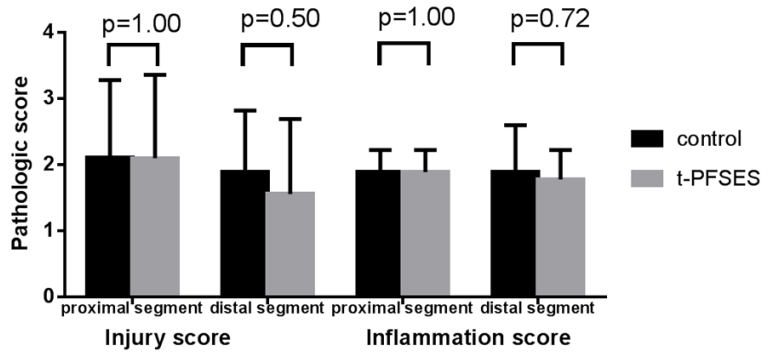

Figure 9. 6 month pathologic score.

ments and, as a result, a greater injury score and neointima 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 avoiding 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.

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 [9, 18, 19], and that polymer-free stents were not associated with persistent inflammation and the "late catch up" phenomenon [20-25], suggesting the polymer is the underlying culprit for the deleterious effects. However, it has been speculated that polymer-free stents might not be released the anti-restenotic drug in the local area for a long enough period to exhibit anti-restenotic effect [22-27]. Indeed, Byrne et al. found that adding a second antiproliferative agent, probucol that targeted a different part of the cell cycle, improved the anti-restenotic performance of polymer-free stents. By changing the stent design to a regular nano-porous drug reservoir, Zheng et al. also demonstrated the sustained efficacy and safety of a polymer-free sirolimus eluting stent in an animal study [6]. In the present study, we used the same stent platform with regular nano-porous drug reservoir as Zheng et al., but it was specifically designed for tapering arteries. Compared with the control stent, the t-PFSES demonstrated a constant superiority along the stented segments, and achieved greater benefits in the distal segments (**Figure 10**).

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 pre-clinical 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

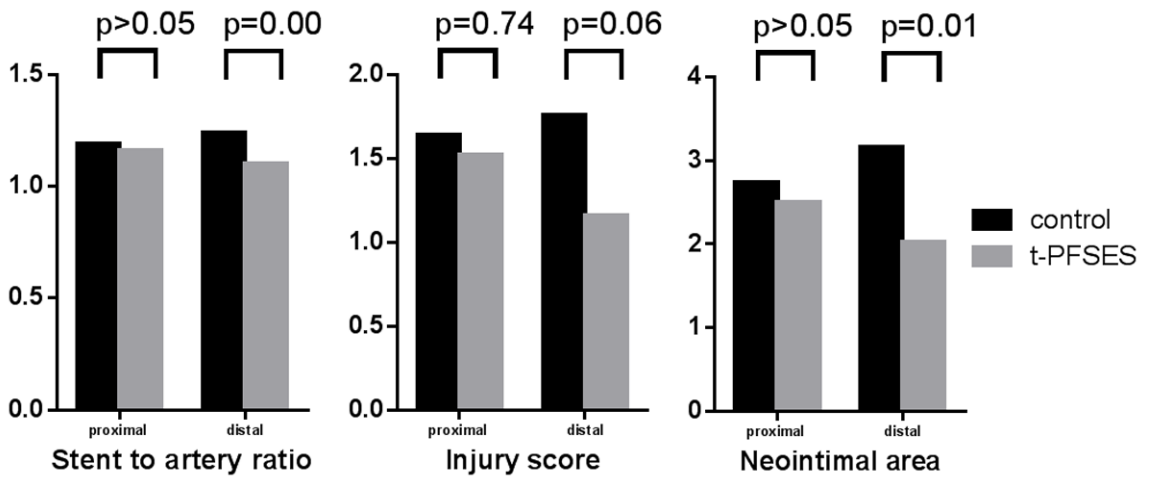

Figure 10. The stent to artery ratio, injury score, neointimal area for control stents and the t-PFSES stents.

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.

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Disclosure of conflict of interest

None.

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References

[1] Zubaid MC, Buller C, Mancini GB. "Normal angiographic tapering of the coronary arteries". Can J Cardiol 2002; 18: 973-980.

[2] Javier SP, Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Leon MB. "Intravascular ultrasound assessment of the magnitude and mechanism of coronary artery and lumen tapering". Am J Cardiol 1995; 75: 177-180.

[3] Banka VS, Baker HA 3rd, Vemuri DN, Voci G, Maniet AR. "Effectiveness of decremental diameter balloon catheters (tapered balloon)". Am J Cardiol 1992; 69: 188-193.

[4] Laird JR, Popma JJ, Knopf WD, Yakubov S, Satler L, White H, Bergelson B, Hennecken J, Lewis S, Parks JM, Holmes DR. "Angiographic and procedural outcome after coronary angioplasty in high-risk subsets using a decremental diameter (tapered) balloon catheter. Tapered Balloon Registry Investigators". Am J Cardiol 1996; 77: 561-568.

[5] Timmins LH, Meyer CA, Moreno MR, Moore JE Jr. "Mechanical modeling of stents deployed in tapered arteries". Ann Biomed Eng 2008; 36: 2042-2050.

[6] Chen M, Zheng B, Wu Z, Peng HY, Wang XG, Zhang B, Huo Y. Efficacy and safety of a novel nano-porous polymer-free sirolimus-eluting stent in pigs. Chin Med J (Engl) 2013; 126: 4731-4735.

[7] Otsuka F, Pacheco E, Perkins LE, Lane JP, Wang Q, Kamberi M, Frie M, Wang J, Sakakura K, Yahagi K, Ladich E, Rapoza RJ, Kolodgie FD, Virmani R. "Long-term safety of an everolimus-eluting bioresorbable vascular scaffold and the cobalt-chromium XIENCE V stent in a porcine coronary artery model". Circ Cardiovasc Interv 2014; 7: 330-342.

[8] Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. "Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model". J Am Coll Cardiol 1992; 19: 267-274.

[9] Carter AJ, Aggarwal M, Kopia GA, Tio F, Tsao PS, Kolata R, Yeung AC, Llanos G, Dooley J, Falotico R. "Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model". Cardiovasc Res 2004; 63: 617-24.

[10] Williams IL, Thomas MR, Robinson NM, Wainwright RJ, Jewitt DE. "Angiographic and clinical restenosis following the use of long coronary Wallstents". Catheter Cardiovasc Interv 1999; 48: 287-293; discussion 294-285.

[11] Roiron C, Sanchez P, Bouzamondo A, Lechat P, Montalescot G. "Drug eluting stents: an updated meta-analysis of randomised controlled trials". Heart 2006; 92: 641-649.

[12] Pfisterer MH, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C; BASKET-LATE Investigators. "Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents". J Am Coll Cardiol 2006; 48: 2584-2591.

[13] Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. "Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials". Am J Med 2006; 119: 1056-1061.

[14] Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. "Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents". N Engl J Med 2007; 356: 998-1008.

[15] Claessen BE, Beijk MA, Legrand V, Ruzyllo W, Manari A, Varenne O, Suttorp MJ, Tijssen JG, Miquel-Hebert K, Veldhof S, Henriques JP, Serruys PW, Piek JJ. "Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial". Circ Cardiovasc Interv 2009; 2: 339-347.

[16] Raber L. "SIRTAX-LATE: five-year clinical and angiographic follow-up from a prospective randomized trial of sirolimus-eluting and paclitaxel-eluting stents". Transcatheter Cardiovascular Therapeutics. San Francisco: CA; 2009.

[17] Aoki J, Abizaid AC, Ong AT, Tsuchida K, Serruys PW. "Serial assessment of tissue growth inside and outside the stent after implantation of drug-eluting stent in clinical trials. -Does delayed neointimal growth exist?" EuroIntervention 2005; 1: 235-255.

[18] Kornowski R, Hong MK, Virmani R, Jones R, Vodovotz Y, Leon MB. "Granulomatous' foreign body reactions' contribute to exaggerated in-stent restenosis". Coron Artery Dis 1999; V10: 9-14.

[19] van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR Jr, Ellis SG, Topol EJ. "Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries". Circulation 1996; 94: 1690-1697.

[20] Grube E. "Biofreedom first in man progress report". transcatheter cardiovascular therapeutics. San Francisco: CA; 2009.

[21] Costa JR Jr, Abizaid A, Costa R, Feres F, Tanajura LF, Abizaid A, Maldonado G, Staico R, Siqueira D, Sousa AG, Bonan R, Sousa JE. "1-year results of the hydroxyapatite polymer-free sirolimus-eluting stent for the treatment of single de novo coronary lesions: the VESTASYNC I trial". JACC Cardiovasc Interv 2009; 2: 422-427.

[22] Mehilli J, Kastrati A, Wessely R, Dibra A, Hausleiter J, Jaschke B, Dirschinger J, Schömig A; Intracoronary Stenting and Angiographic Restenosis-Test Equivalence Between 2 Drug-Eluting Stents (ISAR-TEST) Trial Investigators. "Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss". Circulation 2006; 113: 273-279.

[23] Ruef J, Storger H, Schwarz F, Haase J. "Comparison of a polymer-free rapamycin-eluting stent (YUKON) with a polymer-based paclitaxel-eluting stent (TAXUS) in real-world coronary artery lesions". Catheter Cardiovasc Interv 2008; 71: 333-339.

[24] Mehilli J, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O, Pache J, Wessely R, Schömig A, Kastrati A; Intracoronary Stenting and Angiographic Restenosis Investigators--Test Efficacy of Rapamycin-eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3). "Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis". Eur Heart J 2008; 29: 1975-1982.

[25] Byrne RA, Kufner S, Tiroch K, Massberg S, Laugwitz KL, Birkmeier A, Schulz S, Mehilli J; ISAR-TEST-3 Investigators. "Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results". Heart 2009; 95: 1489-1494.

[26] Byrne RA, Mehilli J, Iijima R, Schulz S, Pache J, Seyfarth M, Schömig A, Kastrati A. "A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents". Eur Heart J 2009; 30: 923-931.

[27] Byrne RA, Kastrati A, Tiroch K, Schulz S, Pache J, Pinieck S, Massberg S, Seyfarth M, Laugwitz KL, Birkmeier KA, Schömig A, Mehilli J; ISAR-TEST-2 Investigators. "2-year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor [corrected] drug-eluting stents". J Am Coll Cardiol 2010; 55: 2536-2543.

[28] Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. "In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia". J Am Coll Cardiol 1998; 31: 224-230.

[29] Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vliestra RE, Holmes DR. "Restenosis after balloon angioplasty. A practical proliferative model in porcine coronary arteries". Circulation 1990; 82: 2190-2200.

[30] Karas SP, Gravanis MB, Santoian EC, Robinson KA, Anderberg KA, King SB 3rd. "Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis". J Am Coll Cardiol 1992; 20: 467-474.

[31] Bezerra H, Perin E, Berger P, Block P, Ramee S, Katz S, Kellet M, Dippel E, Schaer G, Britto S, Cohen S, Costa M. "Outcomes of unselected recipients of sirolimus-eluting stents: the Cypher stent U.S. post-marketing surveillance registry". J Invasive Cardiol 2010; 22: 48-55.

[32] Hoffmann R, Klinker H, damu U, Kelm M, Blindt R. "The risk of definitive stent thrombosis is increased after "off-label" stent implantation irrespective of drug-eluting stent or bare-metal stent use". Clin Res Cardiol 2009; 98: 549-554.

[33] Planer D, Beyar R, Almagor Y, Banai S, Guetta V, Miller H, Kornowski R, Brandes S, Krakover R, Solomon M, Lotan C. "Long-term (>3 Years) outcome and predictors of clinical events after insertion of sirolimus-eluting stent in one or more native coronary arteries (from the Israeli arm of the e-Cypher registry)". Am J Cardiol 2008; 101: 953-959.

[34] Grube E, Dawkins K, Guagliumi G, Banning A, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Joshi A, Mascioli S. "TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, com-

plex coronary artery lesions". EuroIntervention 2009; 4: 572-577.

[35] Tanabe K, Serruys PW, Degertekin M, Guagliumi G, Grube E, Chan C, Munzel T, Belardi J, Ruzyllo W, Bilodeau L, Kelbaek H, Ormiston J, Dawkins K, Roy L, Strauss BH, Disco C, Koglin J, Russell ME, Colombo A; TAXUS II Study Group. "Chronic arterial responses to polymer-controlled paclitaxel-eluting stents: comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS-II trial". Circulation 2004; 109: 196-200.

[36] Aoki J, Colombo A, Dudek D, Banning AP, Drzewiecki J, Zmudka K, Schiele F, Russell ME, Koglin J, Serruys PW; TAXUS II Study Group. "Peristent remodeling and neointimal suppression 2 years after polymer-based, paclitaxel-eluting stent implantation: insights from serial intravascular ultrasound analysis in the TAXUS II study". Circulation 2005; 112: 3876-3883.

[37] Silber S, Colombo A, Banning AP, Hauptmann K, Drzewiecki J, Grube E, Dudek D, Baim DS. "Final 5-year results of the TAXUS II trial: a randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for de novo coronary artery lesions". Circulation 2009; 120: 1498-1504.

[38] Ruiz-Nodar JM, Frutos A, Carrillo P, Morillas P, Valero R, Rodríguez JA, Gallego J, Valls A, Bertomeu V. "Use of sirolimus-eluting stents in complex lesions: clinical and angiographic follow-up". Rev Esp Cardiol 2004; 57: 123-129.

[39] Grube E, Dawkins KD, Guagliumi G, Banning AP, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Popma JJ, Buellesfeld L, Koglin J, Russell ME. "TAXUS VI 2-year follow-up: randomized comparison of polymer-based paclitaxel-eluting with bare metal stents for treatment of long, complex lesions". Eur Heart J 28: 2578-2582.

[40] Varbella F, Gagnor A, Tomassini F, Infantino V, Conte MR. "Immediate and long-term results of treatment of complex lesions of the left anterior descending coronary artery involving a large diagonal branch with drug-eluting stents". J Cardiovasc Med (Hagerstown) 2008; 9: 1088-1094.