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Original Article

The overlap nano-porous polymer-free sirolimus-eluting stent in swine model evaluated by optical coherence tomography and histopathology

Bo Zheng*, Chang Hou*, Xingang Wang, Bin Zhang, Qiuping Shi, Ming Chen

*Department of Cardiology, Peking University First Hospital, Beijing, China. *Equal contributors.*

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Abstract: Objective: A potentially adverse vascular response to overlapping drug eluting stents (DES) has been reported in current research. The performance of polymer-free DES overlap has not been fully investigated. Methods: This is a randomized controlled animal study designed to evaluate the efficacy of overlapping nano-porous polymer-free sirolimus-eluting stents (PFSES) in a swine model. A total of 20 overlapping stents (3.0 mm × 12 mm) were successfully implanted in the right coronary arteries of 10 swine: 10 overlapping PFSES and 10 overlapping polymer-coated sirolimus-eluting stents (PCSES). Animals underwent quantitative coronary angiography (QCA) and optical coherence tomography (OCT) and were terminated at 1 month follow-up for completely histopathologic analyses. End points were late lumen loss, neointimal area, maximum intimal thickness, inflammation score, injury score and endothelialization score of overlapping segment. Results: At 1 month follow-up, QCA analysis indicated that lumen loss of PFSES overlap group was significantly smaller than that of PCSES overlap group (0.55±0.14 mm *vs.* 0.83±0.21 mm, $P = 0.04$). OCT evaluations also showed overlapping PFSES appeared a decreased tendency on the inhibition of neointimal area (2.99±1.19 mm^2 *vs.* 5.01±0.61 mm^2, $P = 0.053$) and maximum intimal thickness (0.52±0.09 mm *vs.* 0.94±0.29 mm, $P = 0.057$) compared with PCSES. Significantly lower inflammation score (1.20±0.55 *vs.* 2.40±0.45, $P = 0.033$) and incidence of heterogeneous neointima (0% *vs.* 80%, $P = 0.048$) were observed in PFSES compared with PCSES group. Notably, injury score and endothelialization were comparable between two groups. Conclusion: The nano-porous polymer-free SES overlap leads to significant inhibition of neointimal hyperplasia and inflammatory cell infiltration compared with overlapping PCSES. Further investigations are needed to validate these findings in clinical trials.

Keywords: Overlap, polymer-free, drug-eluting stent, swine, optical coherence tomography

Introduction

Coronary stent overlap has been widely reported in clinical practice (30% or more of coronary percutaneous coronary intervention [PCI] cases) owing to excessive lesion length, edge dissections, or incomplete stent coverage [1-3]. Clinical trials of overlapping drug-eluting coronary stents (DES) have shown markedly reduced rates of clinical and angiographic restenosis compared to overlapping bare metal stents (BMS) [4-12].

Nevertheless, the long-term safety of polymer coated sirolimus-eluting stent (PCSES) has been called into question owing to concerns about late stent thrombosis secondary to impaired arterial healing characterized by delayed re-endothelialization and persistence of fibrin [13, 14]. Impaired endothelialization of PCSES may result from the persistent drug delivery polymers that provoked inflammatory cell infiltration and led to long-term drug sequestration within the arterial wall [15-17]. Currently, a polymer-free sirolimus-eluting stent with a unique nano-porous surface that allowed drug storage and controlled release was expected to minimize such limitation.

The objective of the present study was to evaluate a novel nano-porous polymer-free sirolimus-eluting stent (PFSES) overlap compared with PCSES in a swine model.

Methods

Stents

Stent surface was visualized by a scanning electron microscope (JSM5510). The polymer-

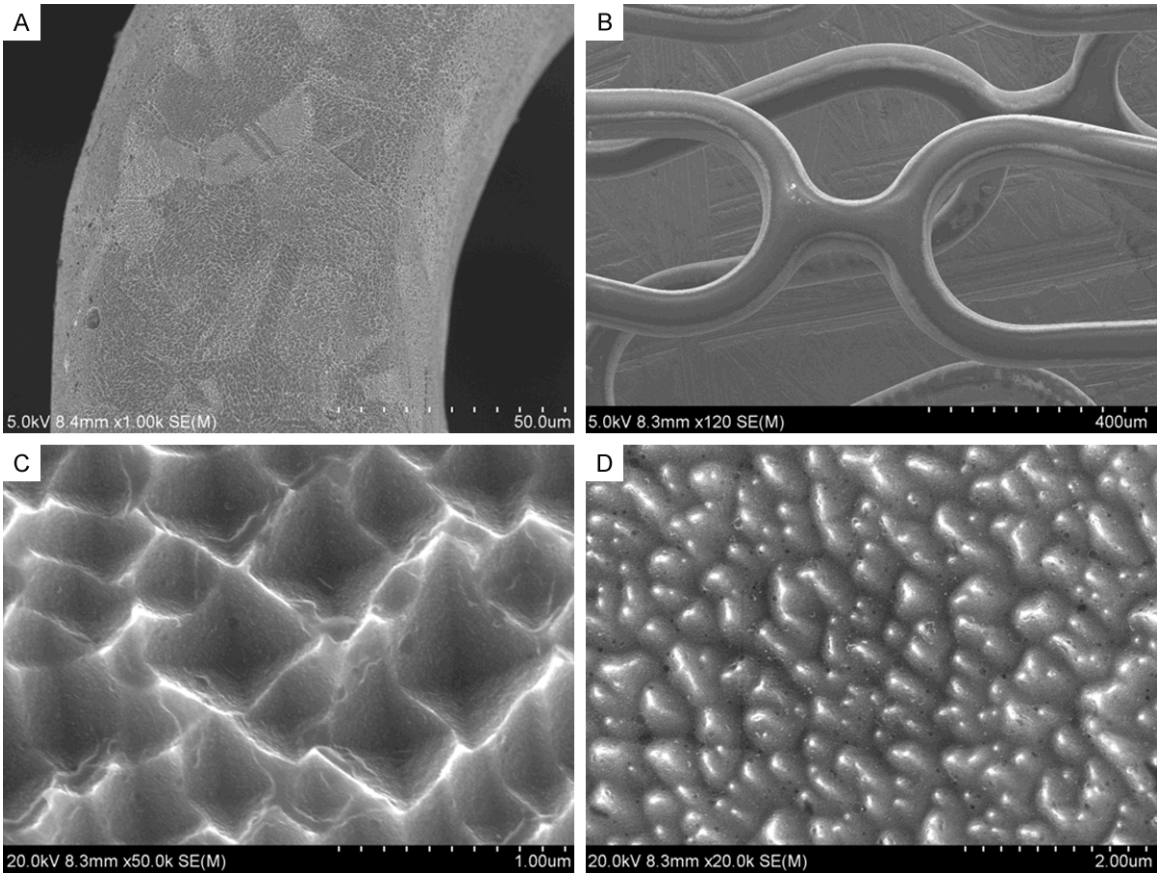

Figure 1. Scanning electron microgram of strut surface. Expanded Polymer-free sirolimus-eluting stent coated with sirolimus at a magnification of ×100 (A) and ×50 (B), visually highlighting uniform drug distribution across the entire stent surface. The stent strut surface before (C) and after (D) sirolimus coating at magnifications of ×10,000 and ×5000, respectively.

free sirolimus-eluting stents used in the experiments were 3.0 mm × 12 mm, made of 316 L stainless steel. 300-500 nm diameter pores were prepared directly on stent strut using electrochemical surface treatment. Polymer-free sirolimus-eluting stent was pre-loaded on the balloon catheter system. The microporous surface of the stent platform allowed for drug deposition and retarded drug release without obligate application of a polymer (**Figure 1**) [18].

Polymer-coated sirolimus-eluting stents (PCSES) (Lepumedical Technology, China) as control group were 3.0 mm × 12 mm, 316 L stainless steel stents, PBMA/PEVA as polymer. Sirolimus loaded on the stent was 1.2 μg/mm^2.

Porcine coronary stent model

Experiments were conducted with permission of the animal protection committee of the local government. Ten Chinese swine with a body weight of 25 to 30 kg were used. Since three days before percutaneous intervention, juvenile swine received a 75 mg of clopidogrel and 500 mg of aspirin every day. The antiplatelet therapy of 75 mg clopidogrel and 250 mg of aspirin was maintained throughout the study. During the procedure, the animals received 200 IU/kg body weight of heparin intravenously. A total of 10 fully anesthetized and ventilated swine underwent stent implantation in right coronary artery (RCA). A total of 20 coronary stents was randomly deployed in the RCA at a stent-to-vessel ratio of 1.2-1.3:1 with PCSES (n = 10), and PFSES stents (n = 10) without hybrid implantation.

Two stents of the same type were overlapped in the right coronary arteries of each swine, and the overlap was 6 mm. The animals remained well throughout the study without abnormal

Table 1. Quantitative coronary analysis at baseline and 1-month follow-up

	PFSES overlap	PCSES overlap	*P* value
Reference artery diameter, mm	2.9±0.09	2.92±0.18	0.91
Balloon/artery ratio	1.18±0.43	1.2±0.22	0.75
Post-procedure MLD, mm	3.34±0.83	3.42±0.68	0.69
Follow-up MLD, mm	2.8±0.77	2.61±0.92	0.34
Late lumen loss, mm	0.55±0.14	0.83±0.21	0.04

MLD indicates minimum lumen diameter.

temperature, weight loss, or other major health problems.

Imaging acquisition and analysis

Quantitative coronary angiography (QCA) evaluation was performed in the overlapped segments of each stenting vessel. Angiograms recorded before and immediately after the procedure as well as at 1 month were assessed with the aid of the quantitative angiographic analysis software (INOVA 2100 GE Company, USA). Late lumen loss was the difference in the minimal lumen diameter (MLD) between that immediately after the procedure and that at 1 month. QCA (GE Company, USA) evaluation was performed right at 1 month after procedure.

At 1 month, optical coherence tomography (OCT) imaging was performed with an occlusion balloon (Helios™, LightLab Imaging) and an OCT catheter (Image Wire™, LightLab Imaging, Westford, MA, USA). An automatic pullback of the OCT catheter was initiated at a speed of 1 mm/s with recording of OCT images. The area of both the lumen and stent was measured every 1 mm. Lumen area, stent area, neointimal area (stent area minus lumen area), the percent of neointimal area (ratio of neointimal area and stent area, multiplied by 100) and maximum neointimal thickness were also calculated [19].

Histology

At 1 month after stent implantation, all swine were sacrificed. For histological analysis, the heart was removed and rinsed through the ostium of the RCA with 250 mL 0.9% NaCl at physiological pressure, followed by perfusion fixation using 10% formaldehyde for each coronary artery. Subsequently, stented artery segments were removed and fixed for another 24 hours in 10% formaldehyde solution. After a dehydration protocol for several days, stented vessels were embedded in methylmethacrylate as previously described. For histomorphometric analysis, 5 μm-thick sections were cut with a LEIKA SP1600 microtome, stained according to the hematoxylin and eosin (HE) technique, and scanned with a Leica DFC300FX microscope. Morphometric analysis was performed by Leica Qwin Plus V3.2.1 software, Leica, DM LB2 DFC300FX. For additional assessment of inflammation, 1 embedded segment of each implanted stent was HE-stained according to an established protocol and analyzed at a thickness of 5 μm according to established scores. Assessment score for strut-associated inflammation: 0 = none; 1 = scattered inflammatory cells; 2 = inflammatory cells encompassing 50% of a strut in at least 25% to 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 [20]. Stent endothelialization was defined as the extent of the circumference of the arterial lumen covered by endothelium: 1 = 25%; 2 = 25% to 75%; and 3 = 75% to 100% coverage [21]. Injury score: 0 = complete internal elastic lamina (IEL); 1 = broken IEL; 2 = broken IEL and media; 3 = broken external elastic lamina (EEL) [14].

Statistical analysis

Categorical variables are presented as frequencies and compared with X^2 statistics or Fisher's exact test (if there was an expected cell value < 5); continuous variables are presented as means ± standard deviation and compared using Mann-Whitney U test by using SPSS 13.0 software. Differences among experimental groups were considered to be statistically significant when $P < 0.05$.

Results

Safety and efficacy of polymer-free sirolimus-eluting stents overlap compared with polymer-coated sirolimus-eluting stents overlap in vivo

In each group, all animals survived until 1 month follow-up and there was no evidence of

Table 2. Optical coherence tomography analysis at 1-month follow-up

	PFSES overlap	PCSES overlap	*P* value
Mean lumen area, mm^2	5.88±1.08	4.85±0.99	0.91
Mean stent area, mm^2	8.87±0.88	9.86±0.89	0.75
Mean neointimal area, mm^2	2.99±1.19	5.01±0.61	0.053
Neointimal proliferation, %	39.7±12.8	65.1±22.4	0.06
Maximum neointimal thickness, mm	0.52±0.09	0.94±0.29	0.057

acute or subacute stent thrombosis. Swine were monitored by veterinarians, reporting no evidence for increased infections or any other serious acknowledge.

QCA and OCT analysis

At baseline, the reference artery diameter and balloon-to-vessel ratio were comparable between the two groups. At 1 month post-implantation, late lumen loss significantly decreased by PFSES overlap compared with PCSES overlap (0.55±0.14 mm *vs*. 0.83±0.21 mm, *P* = 0.04) by QCA analysis (**Table 1**).

Compared with PCSES overlap, polymer-free SES overlap appeared a decreased tendency of the inhibition of neointimal growth. Although, the neointimal hyperplasia was numerically greater in PCSES group compared with those with PFSES deployment, there was no significant difference between PFSES and PCSES overlap on mean neointimal area (2.99±1.19 mm^2 *vs*. 5.01±0.61 mm^2 respectively, *P* = 0.053), % neointimal hyperplasia (39.7%± 12.8% *vs*. 65.1%±22.4%, *P* = 0.06), maximum intimal thickness (0.52±0.09 mm *vs*. 0.94± 0.29 mm, *P* = 0.057) by OCT analysis (**Table 2**). Notably, lower incidence of heterogeneous neointima (0% *vs*. 80%, *P* = 0.048) was observed in overlapping PFSES compared with PCSES group (**Figure 2**).

Histomorphometry

At 1 month, the inflammation score was significantly lower in overlapping PFSES compared with the overlapping PCSES group (1.20±0.55 *vs*. 2.40±0.45, *P* = 0.033) (**Figure 3**). However, injury score was comparable between the two groups. Moreover, at 1 month, both overlap of PFSES and PCSES showed complete endothelialization (**Figure 3**).

Discussion

Stent overlap has been widely used in effective coverage of challenging coronary lesions including long lesions and complex vessel anatomy [22]. DES have shown great advantages over BMS in the incidence of neointimal hyperplasia, angiographic restenosis, target-lesion revascularization and major adverse cardiac events while delay arterial healing and increase the risk of late stent thrombosis as well [1-3, 8, 9, 23]. In our present study, the main findings were: 1) At 1 month follow-up, lumen loss in PFSES overlap group were significantly lower than those of PCSES overlap; overlapping PFSES appeared a decreased tendency on the inhibition of neointimal area and maximum intimal thickness. 2) Inflammatory reaction and immature neointimal hyperplasia were less likely to develop in the PFSES overlap group than those with overlapping PCSES deployment.

Lesion length, longer stented segment, multiple stent placement as well as overlapping stents were identified as the risk factors of restenosis [5, 6, 10, 11]. John *et al.* reported that polymer-free sirolimus-eluting stents and polymer-free sirolimus-eluting stents plus estradiol resulted in less robust neointimal suppression compared with Cypher drug-eluting stents in a rabbit iliac model of overlapping stent placement [24]. Similarly, significant reduction of lumen loss and a decreased tendency of the inhibition of neointimal growth were observed in PFSES overlap group by QCA and OCT evaluations in present study. These findings underscore the important role that polymers may play in neointimal suppression. Longer time follow-up is needed because long-term inhibition of neointimal hyperplasia may not be sustained for the sirolimus-eluting stents as previously reported in TAXUS overlap [17, 25]. Moreover, Norio *et al.* reported that the polymer-free Biolimus A9-coated stent demonstrated equivalent early and superior late reduction of intimal proliferation compared with polymer-coated SES in a porcine model [26].

The biological arterial response to DES is likely based on the unique properties of the polymer

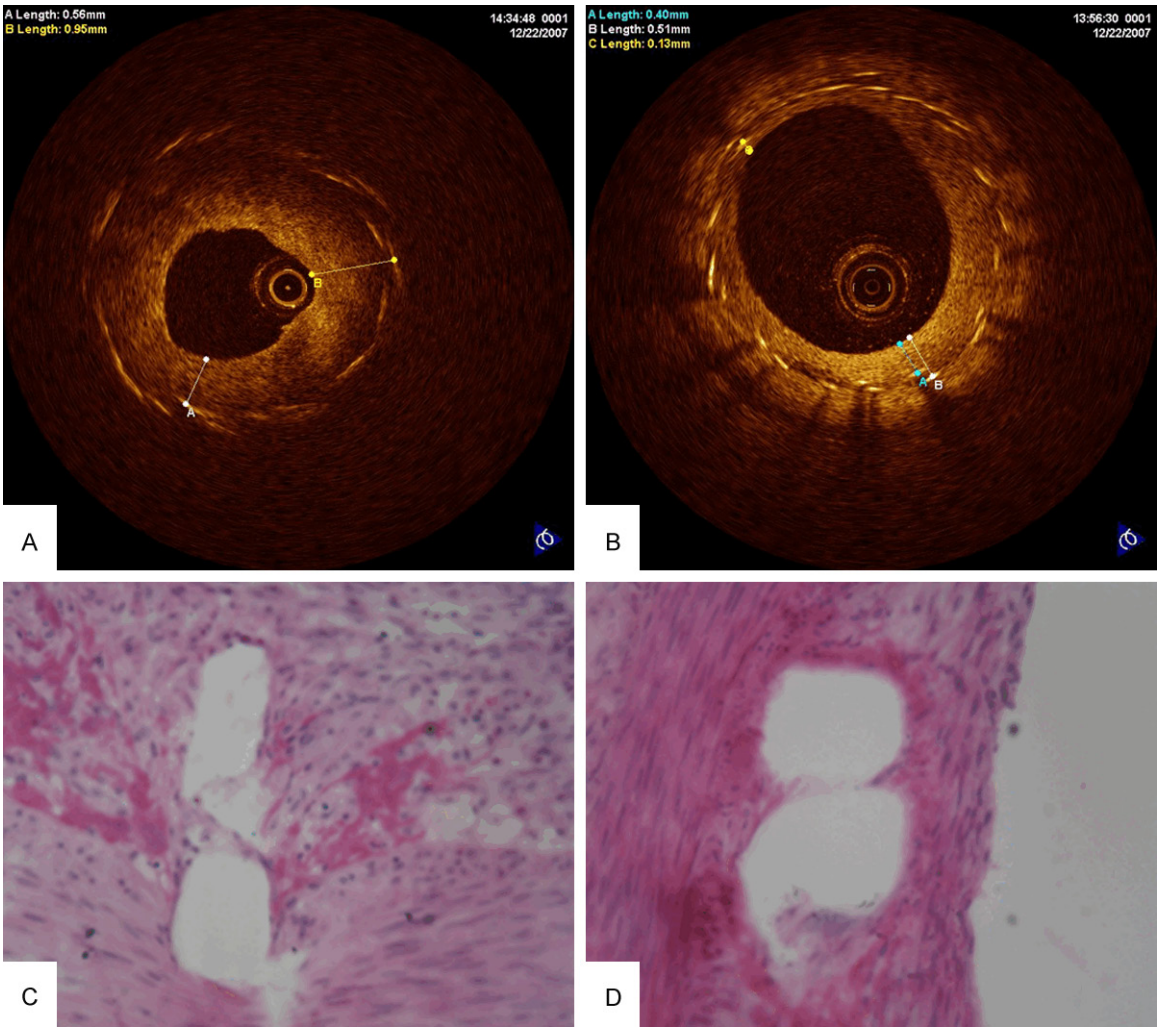

Figure 2. Representative optical coherence tomography imaging and histological.

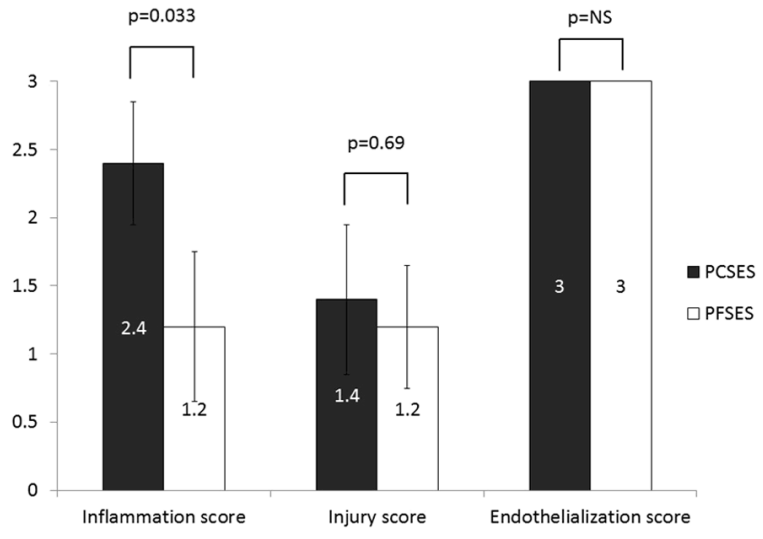

Figure 3. The comparison of inflammation score, injury score and endothelialization score between polymer-free sirolimus-eluting stent and polymer-coated sirolimus-eluting stent.

and/or drug combination, in addition to the increased metal load at the overlap. Finn *et al.* examined the arterial reaction to overlapping Cypher or Taxus drug-eluting stents in rabbits with bare metal stents, serving as controls for the first time. Overlapped segments exhibited delayed healing compared with proximal and distal nonoverlapping sites at 28 days [15]. Similar result was also seen in the juvenile farm swine, 25-35 kg in weight, 3-6 months in age overlap stents model [27] and DES implantation autopsies of 30 days duration characterized by persistent fibrin deposition and

poorer endothelialization [14]. The delayed healing may be attributed to either theoretical doubling in drug release or tissue contact with coating polymer, while the result of our own study that inflammation score was significantly lower in overlapping PFSES suggested the important role of polymer in this process. This speculation can be further supported by the evidence that an array of polymer has been demonstrated to induce a marked inflammatory reaction within the coronary artery [28] and that higher dose of polymer coat causes more severe strut-associated inflammation indicating a possible bulk effect [22]. Notably, the proportion of heterogeneous neointimal hyperplasia was significantly higher in the overlapping PCSES group, indicating inflammatory cell infiltration, especially for the macrophages [29]. The vascular response to ongoing injury and inflammation induced by the residual polymer may simply overwhelm the biological effects of the drug and result in the subsequent formation of neointima [17, 28], which may be the reason of larger neointimal area and maximum intimal thickness in PCSES group in present study.

Late stent thrombosis has been another concern for DES, the cause of which is multifactorial including delayed arterial healing and additional procedural and pathologic risk factors such as local hypersensitivity reaction, ostial and/or bifurcation stenting, malapposition, incomplete lesion coverage, excessive stent length, or cessation of antiplatelet therapy [3, 14]. Poor endothelialization occurring at the site of overlapping drug-eluting stents was reported in a porcine model of in-stent restenosis [30]. To the best of our knowledge, the mechanism of delayed endothelialization after DES overlap is that the overlapping increases the local drug concentration by changing the cell structure of the stent strut and the overlap itself. Nevertheless there was no evidence of acute or subacute stent thrombosis and endothelialization of two groups was comparable at 1 month in present study, which was consistent with overlapping Taxus porcine model previously reported [25]. However, further investigation with larger sample and different timing is needed to validate the current findings.

The relative small sample size may lead to type I statistical error. Given that the animals in present study are normal without atherosclerosis and that lipid within the stented atherosclerotic plaque may also influence drug distribution and retention, prolonged compound tissue retention leading to long-term biological effects may be underestimated. Also, limited follow-up timing did not provide adequate information about natural history and long-term effect of PFSES overlap.

In current pilot study, the nano-porous polymer-free SES overlap lead to significant reduction of neointimal formation and inflammatory reaction compared with overlapping PCSES, indicating that the polymer-free SES might have potential benefit over polymer-based DES. Further investigations are needed to validate these findings in clinical evaluation and practice.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ming Chen, Department of Cardiology, Peking University First Hospital, 8 Xishiku St., Xicheng District, Beijing 100034, China. Tel: +86 (10) 6655-1122 Ext. 2283; E-mail: cm6141@sina.com

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