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PRE-CLINICAL RESEARCH

Vasomotor Function After Paclitaxel-Coated Balloon Post-Dilation in Porcine Coronary Stent Model

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Objectives The purpose of this study was to evaluate endothelial function after post-dilation of bare-metal stents with paclitaxel-coated balloons (PCB) or non–drug-coated balloons (non-DCB) in a porcine model.

Background DCB are an attractive alternative to drug-eluting stents because they provide short duration of drug exposure, while potentially inhibiting in-stent restenosis. Drug-eluting stents are associated with impaired endothelial function. It is unknown whether this abnormal vasomotor function is mitigated by reduced duration of drug exposure.

Methods Thirteen pigs underwent bare-metal stent implantation (arteries, n = 30), followed by post-dilation with either PCB (SeQuent Please, B. Braun Melsungen AG, Berlin, Germany) (n = 17) or non-DCB (n = 13). Five pigs with unstented arteries (n = 14) were controls. Coronary vasomotion was assessed 1 month after stent implantation, using acetylcholine (Ach) and nitroglycerin. Measurements were obtained for distal segments.

Results Angiographic late loss and histological area stenosis were similar between PCB and non-DCB. However, the percentage of diameter change in response to Ach was diminished with PCB ($p < 0.05$), when compared with either non-DCB or naive arteries. There was no difference between non-DCB and naive arteries. Inflammatory score and intramural fibrin grading were significantly greater in PCB than non-DCB ($p < 0.05$). Additionally, inflammatory cell infiltration in the stented segments correlated with the degree of percentage of diameter change in response to Ach, at distal regions.

Conclusions Post-dilation of bare-metal stents with PCB was associated with impaired vasodilatory response to Ach distal to the treated segments. Vasodilatory response after post-dilation with non-DCB was similar to control arteries. (J Am Coll Cardiol Intv 2011;4:247–55) © 2011 by the American College of Cardiology Foundation

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The use of drug-eluting stents (DES) results in reduced in-stent restenosis and target lesion revascularization compared with bare-metal stents (BMS) (1–3). Significant clinical issues remain, including delayed arterial healing, impaired re-endothelialization, prolonged requirement for dual antiplatelet therapy, as well as late and very late stent thrombosis (4–7). This has influenced clinical practice, in that there was a 20% decline between 2006 and 2008 in the use of DES for non–ST-segment elevation myocardial infarction patients (8).

Local drug delivery via a drug-coated balloon (DCB) has been proposed as a potential solution to the cellular proliferative response stimulated by the implantation of stents. Delivery of an antiproliferative drug, which could achieve maximal concentration of therapeutic bioactive agent within the stented arterial wall, might minimize systemic side effects, reduce drug-artery exposure time, obviate the need for polymer coating on stents, and circumvent the complications of DES.

Abbreviations and Acronyms

Ach = acetylcholine
BMS = bare-metal stent(s)
D1 = diameter of segment 5 to 10 mm distal to stent
D2 = diameter of segment 10 to 15 mm distal to stent
DCB = drug-coated balloon(s)
DES = drug-eluting stent(s)
INTG = nitroglycerin
PCB = paclitaxel-coated balloon(s)

Paclitaxel is a lipophilic drug, which allows retention in the artery wall and rapid cellular uptake despite short exposure duration (9). It suppresses proliferation and migration by inhibition of microtubular disassembly and cellular function (10–13). Therefore, paclitaxel is a candidate for use on DCBs. Pre-clinical evaluation (14) and clinical trials have demonstrated that paclitaxel-coated balloons (PCB) can provide adequate drug concentration in the artery wall and reduce neointimal growth with continued benefit for up to 2 years (15–18).

Several studies have demonstrated abnormal vasomotor function after first-generation DES 6 to 12 months after implantation (19–23). These effects have been attributed to local toxicity, inflammation, delayed healing, and oxidative stress. Vasomotor function after PCB administration has not been evaluated. We therefore investigated endothelial-dependent and -independent vasomotion after PCB treatment in a porcine coronary BMS model.

Methods

Study devices. The SeQuent Please (B. Braun Melsungen AG, Berlin, Germany) PCB was used for local delivery of paclitaxel. It was formulated with 3 $\mu g/mm^2$ of paclitaxel film, with iopromide as a hydrophilic spacer, on a total balloon length of 17 mm. Previously published animal data indicate that more than 90% of the drug is released into the arterial wall with balloon inflation (24). The non-DCB (Powersail RX, length 17 mm, Abbott Vascular, Redwood City, California) and the BMS (MULTI-LINK VISION, length 15 mm, Abbott Vascular) were commercially purchased.

Experimental design. Animal handling and care followed the recommendations of the National Institute of Health guide for care, and use of laboratory animals was consistent with guidelines of the American Heart Association. All protocols were approved by the Animal Care and Use Committee and were consistent with Association for Assessment and Accreditation of Laboratory Animal Care guidelines.

Eighteen Yorkshire farm pigs (33.6 ± 3.1 kg) were enrolled in this study. The 13 animals that underwent coronary stent implantation received a combination of 81 mg of aspirin and 75 mg of clopidogrel by mouth daily, which started 3 days before stent implantation and continued until termination. All pigs were fasted overnight before procedures. The animals were sedated with an intramuscular injection of ketamine 20 mg/kg, xylazine 2 mg/kg, and atropine 0.05 mg/kg. After intubation, general anesthesia was induced and maintained with isoflurane (2.5%). Electrocardiographic and blood pressure monitoring were performed throughout the procedures.

Per standard protocol of our group (25), after full heparinization (200 U/kg), cardiac catheterization and stents were implanted. Quantitative coronary angiography guidance was used to obtain a stent-to-artery diameter ratio of 1.1:1. Thirteen pigs underwent BMS implantation followed by post-dilation with either PCB (arteries, n = 17) or conventional non-DCB (arteries, n = 13). Not all arteries in all pigs were used, due to lack of appropriately sized arterial segments to achieve the specified stent-to-artery ratios, or due to lack of an adequate length of distal bed to perform vasomotion testing. The balloon-to-artery diameter ratio was 1.2:1, and the inflation time was 30 s, which was within the manufacturer's suggested duration range. Both PCB and non-DCB were slightly longer than the stents (2 mm) to ensure complete coverage of the entire stented segment. To obtain valid information, animals were randomized to balloon type, and each pig was treated with only 1 type of balloon. The remaining 5 animals (arteries, n = 14) were used for naive controls, and only vasomotor function testing was performed at 28 days.

At 1 month, endothelium-dependent coronary vasomotor function was assessed after infusion of incremental acetylcholine (Ach) doses (10^{-7} and 10^{-6} mol/l/ml) and nitroglycerin (NTG) (200 μg). After engagement of a 6-F coronary guide catheter, a 2.3-F infusion catheter (UltraFuse, Boston Scientific, Natick, Massachusetts) was advanced into the proximal portion of the stented artery. After baseline angiography, Ach was infused at 1 ml/min for 2 min, with precisely 5-min intervals between each injection. The same volume was injected for each Ach administration. Coronary angiography was performed 30 s after Ach infu-