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Nobori Stent Shows Less Vascular Inflammation and Early Recovery of Endothelial Function Compared With Cypher Stent

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Objectives The current study sought to examine inflammation at the stented segments of Nobori (Terumo Corporation, Tokyo, Japan) and Cypher (Cordis, Miami, Florida) drug-eluting stents (DES), as well as free radical production and endothelial function of the adjacent nonstented segments in a pig coronary model.

Background Nobori is a novel DES, incorporating a biolimus A9-eluting biodegradable polymer coated only on the abluminal surface of the stent. These unique features may favorably affect inflammation and endothelial function, as compared to the currently marketed DES. Presently, preclinical data on direct comparison of the various generations of DES are not available.

Methods A total of 18 DES were implanted in pig coronary arteries and subsequently explanted at 1 month. Stented segments were assessed by angiography and histology. Ex vivo vasomotor function and superoxide production in segments proximal and distal to the stent were determined. The vasoconstriction, endothelial-dependent relaxation, and endothelial-independent relaxation of proximal and distal nonstented segments were measured.

Results Histological evaluation revealed lower inflammatory response with Nobori than with Cypher DES. There is trend for lower angiographic percentage diameter stenosis in Nobori versus Cypher groups ($p = 0.054$). There was increased endothelium-dependent relaxation, decreased endothelin-1–mediated contraction, and less superoxide production in the vessel segments proximal and distal to Nobori versus Cypher stents.

Conclusions Our data show significantly lower inflammatory response in the stented segments, and rapid recovery of endothelial function of peristent segments in the Nobori group compared with Cypher DES group at 1 month in porcine coronary artery model. (J Am Coll Cardiol Intv 2012;5: 436–44) © 2012 by the American College of Cardiology Foundation

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Development and widespread use of drug-eluting stents (DES) has provided a novel and efficacious treatment for coronary artery disease, allowing for localized elution of neointimal-inhibiting drugs, thereby reducing in-stent restenosis and target lesion revascularization rates compared with bare-metal stents (BMS) (1,2). However, numerous reports have suggested increased incidences of late stent thrombosis and very late stent thrombosis with the first-generation DES, especially after discontinuation of dual antiplatelet therapy (3,4). Although many factors, such as patient, lesion, as well as procedural characteristics are likely contributory, clinical, histopathologic, and pathophysiological studies have indicated that delayed arterial healing and poor re-endothelialization may play a major role in the pathogenesis of late stent thrombosis (5,6). The possible interaction of the potent antiproliferative agent and permanent nonbiodegradable synthetic polymer have raised concerns regarding delayed arterial healing and poor re-endothelialization, persistent inflammatory responses that may lead to impaired endothelial function at and adjacent to the stent site (5–7).

Potential etiologies and molecular mechanisms of this complex phenomenon (endothelial dysfunction) after DES implantation remain incompletely defined. Multiple factors may be involved, including direct toxic effect from the entrapped drug and/or an acute or delayed hypersensitivity reaction from the polymer and/or drug. Accordingly, we hypothesized that the endothelium-dependent vasomotor functional responses of coronary artery segments proximal and distal to the stent implantation site may be affected during and after the period of drug release. The new polymers and/or drugs with enhanced biocompatibility may reduce inflammation and its attendant effects.

Thus, the purpose of the present study is to assess the vasomotor function of the adjacent coronary conduit vessel segments proximal and distal to the stent implantation site along with inflammatory response to Nobori (Terumo Corporation, Tokyo, Japan) and Cypher (Cordis, Miami, Florida) stents in a pig coronary model.

Methods

A total of 18 DES were implanted into the coronary arteries of 8 farm pigs and subsequently explanted at 1 month. The stent/vessel diameter ratio was approximately 15%. All 18 DES (Cypher, n = 9 and Nobori, n = 9) were blindly assessed for histology of the stented segment and vasomotor function and superoxide production of vascular segment proximal and distal to stent. Vasoconstriction, endothelial-dependent relaxation, and endothelial-independent relaxation were measured.

Stent implant protocol. Pigs received 81-mg acetylsalicylic acid and 75-mg clopidogrel daily for 3 days before stent implantation and then daily afterward until the termination. All pigs were fasted overnight before stent implant procedure. They were sedated by 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%). Electrocardiogram and blood pressure were continuously monitored. Nobori (Terumo Corporation) and Cypher (Cordis) stents were identical in size and length (3.0 to 3.5/23 to 28 mm). With systemic heparin (200 U/kg) administration, activated clotting time measurements were performed. Eighteen stents were respectively implanted in the pig coronary arteries using quantitative coronary angiography, to obtain stent/artery ratio ~1.15:1. Additional inflations were performed based on the target site diameter. Angiographic target-vessel diameter, stent-to-arterial diameter ratio, and post-stent minimal lumen diameter were measured in all animals at implantation.

Angiography, termination, and tissue harvest. All pigs underwent repeat angiographic evaluation (with heparin anticoagulation) 1 month after implantation to determine the late lumen loss and percentage diameter stenosis. After angiographic follow-up restudy, pigs were terminated by exsanguination while still under anesthesia. The heart was immediately harvested and placed into 4°C Kreb solution freshly prepared every day (in mmol/l: NaCl, 120; $MgSO_4$, 1.17; KH_2PO_4, 1.18; $NaHCO_3$, 25.0; $CaCl_2$, 2.5; KCl, 4.7; glucose, 5.5 in the presence of 10 μmol/l indomethacin at pH 7.40). The arterial segments proximal and distal to the stented segment were dissected for vasomotor function and superoxide production. The vascular segment sample that is immediately adjacent to the stent was used for superoxide production studies, and farther segments were used for the vasoreactivity studies (8).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
IEL = internal elastic lamina
NO = nitric oxide
VM = Verhoeff-Masson Trichrome

Subsequently, the heart was again immediately placed into 4°C Kreb solution. The heart was washed to clear the blood and then photographed. The stented portions of the vessels were processed and embedded in methyl methacrylate resin. Each block was trimmed and oriented to obtain transverse 5-μm thick sections of the vessel, using a heavy-duty tungsten-carbide blade. Sections from proximal, medial, and distal vessel portions were mounted on glass slides, deplasticized, and stained with hematoxylin-eosin and Verhoeff-Masson Trichrome (VM) stain (Sigma-Aldrich, St. Louis, Missouri) for visualization and histopathological evaluation.

Endothelial function proximal and distal to the stented segments. Hearts were washed in 4°C Kreb solution. The conduit coronary arterial segments proximal and distal (~5 mm) to the stent were carefully dissected and cleaned of connective tissue. The vessels were cut into 4-mm long segments. Vessel rings were suspended in individual organ

chambers (Radnoti Glass Technology Inc., Monrovia, California).

Vasoconstriction was induced by addition of 40-mmol/l KCl twice followed by 100-mmol/l KCl to the organ chamber. Rings were contracted with prostaglandin $F_{2\text{-alpha}}$ until reaching a stable contraction plateau (~7 min). The rings were then exposed to various concentrations of endothelium-dependent (substance P) and endothelium-independent (sodium nitroprusside) vasodilators. With incubation of N^G-nitro-L-arginine methyl ester for 30 min, endothelium-dependent relaxation response was repeated with substance P. At the end of the study, the rings were contracted by endothelin-1. Between the dose responses, the rings were washed for 45 min. Isometric tension was digitized, acquired, and analyzed using a PowerLab (ADInstruments Inc., Colorado Springs, Colorado).

Measurement of superoxide production proximal and distal to stented segments. Superoxide productions in the conduit coronary arterial segments proximal and distal to the stent were performed using a luminometer (8). Free radical production $O_2^{\cdot -}$) was assessed by the lucigenin chemiluminescence method using a tube luminometer (FB 12, Zylux Corporation, Maryville, Tennessee).

Histopathology. The histological specimens were excised from the proximal, middle, and distal potions of each stent. Histological sections were evaluated at high magnification using bright field microscopy. Proximal, middle, and distal sections of stented arterial segments were scored for inflammation. The following specific morphological criteria were evaluated for each section using a semiquantitative rating scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe, where 0 represented the lowest response and 3 represented the highest response of all tissues analyzed in this study within each category.

Histomorphometry. Morphometric analysis was performed by computer-assisted planimetry on proximal, middle, and distal section cuts from each stented vessel. Low-magnification digital images of VM-stained sections were recorded. The lumen, internal elastic lamina (IEL), and external elastic lamina were traced and area measurements obtained; the areas of the neointima and media were obtained by subtraction of the lumen from the IEL and IEL from external elastic lamina, respectively. The neointimal thickness at each stent strut site was measured as well. The injury score was measured in 3 stented segments and then averaged in each vessel using the Schwartz et al. method (9). The histological percentage area stenosis was calculated according to the following formula: [1 − (luminal area/IEL area) × 100].

Statistics. All data were expressed as mean ± standard error. Statistical analysis was performed by Student *t* tests between the Cypher and Nobori groups. Non-numerical data (such as histopathologic scoring) were expressed as median with quartile ranges and compared using rank-sum tests between groups. A p value < 0.05 was considered significant between groups.

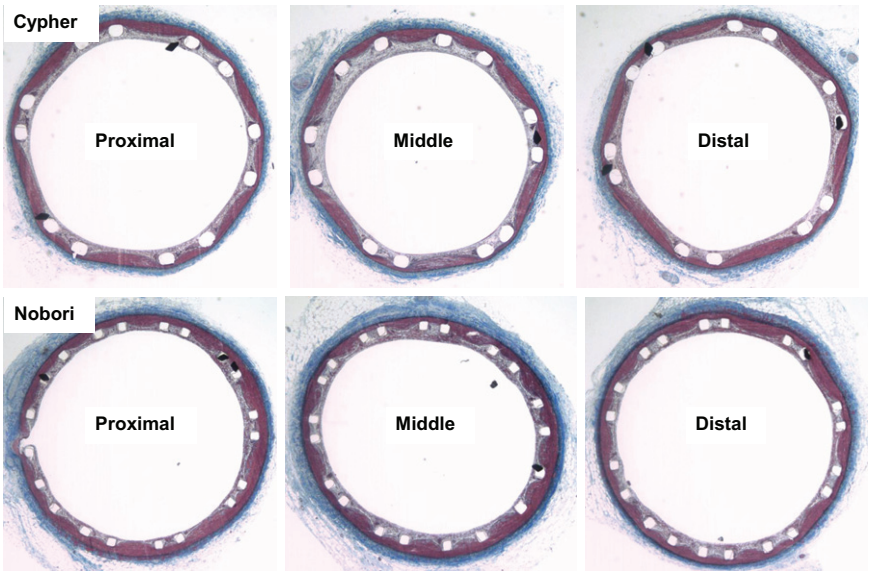

Figure 1. Low Magnification Microscopic Images of Cypher and Nobori Stent Sections

The representative low magnifications microscopic images (20×) of sections stained with Verhoeff-Masson Trichrome stain from coronary segments implanted with Cypher and Nobori stents.

Results

A total of 18 DES stents were implanted in native coronary arteries. The average body weight of the animals was 51.8 ± 1.8 kg at initial implantation and 62.2 ± 1.6 kg at termination.

Angiographic evaluation. Nine Cypher stents were implanted in the left anterior descending (n = 3), left circumflex (n = 3), and right coronary (n = 3) arteries, respectively. Nine Nobori stents were deployed in left anterior descending (n = 3), left circumflex (n = 1), and right coronary (n = 5) arteries, respectively. The respective target vessel diameters (2.99 ± 0.09 and 3.01 ± 0.07; p = 0.85) and the baseline stent/artery ratios (1.13 ± 0.02 and 1.17 ± 0.02; p = 0.20) were similar between Cypher and Nobori groups. At 1 month after implantation, there is a strong trend for lower mean angiographic percentage stenosis in the Nobori group than in the Cypher group (4.0 ± 2.6% vs. 25.5 ± 10.0%, respectively; p = 0.054).

Histopathology and histomorphometry. Stented and nonstented coronary segments (proximal and distal to stented segment), were carefully dissected from perivascular connective and fat tissue. All 9 Nobori stents were easily isolated from the surface of the myocardium without any difficulties. Three of the 9 Cypher coronary segments displayed evidence of inflammation, with diffuse reddish discoloration as well as severe fibrosis around the stents.

The representative low-magnification microscopic images of VM-stained sections from coronary segments implanted with Cypher and Nobori stents are shown in Figure 1.

All histopathologic scoring was performed using high magnification (54 sections). The injury score was 1.02 ± 0.01 in the Nobori group and 1.20 ± 0.10 in the Cypher group (p = 0.098). The Nobori group showed significantly lower inflammation (Grade 1: 93% and Grade 2: 7% in Nobori vs. Grade 1: 48%; Grade 2: 22%, and Grade 3: 30% in Cypher; p < 0.001) (Fig. 2) than the Cypher group.

All histomorphometric parameters were measured using low-magnification VM specimens (54 sections). There were no significant differences in neointimal area (1.63 ± 0.21 mm^2 in Nobori vs. 2.85 ± 0.69 mm^2 in Cypher; p = 0.251), luminal area (5.72 ± 0.24 mm^2 in Nobori vs. 5.03 ± 0.58 mm^2 in Cypher; p = 0.295), IEL area (7.34 ± 0.22 in

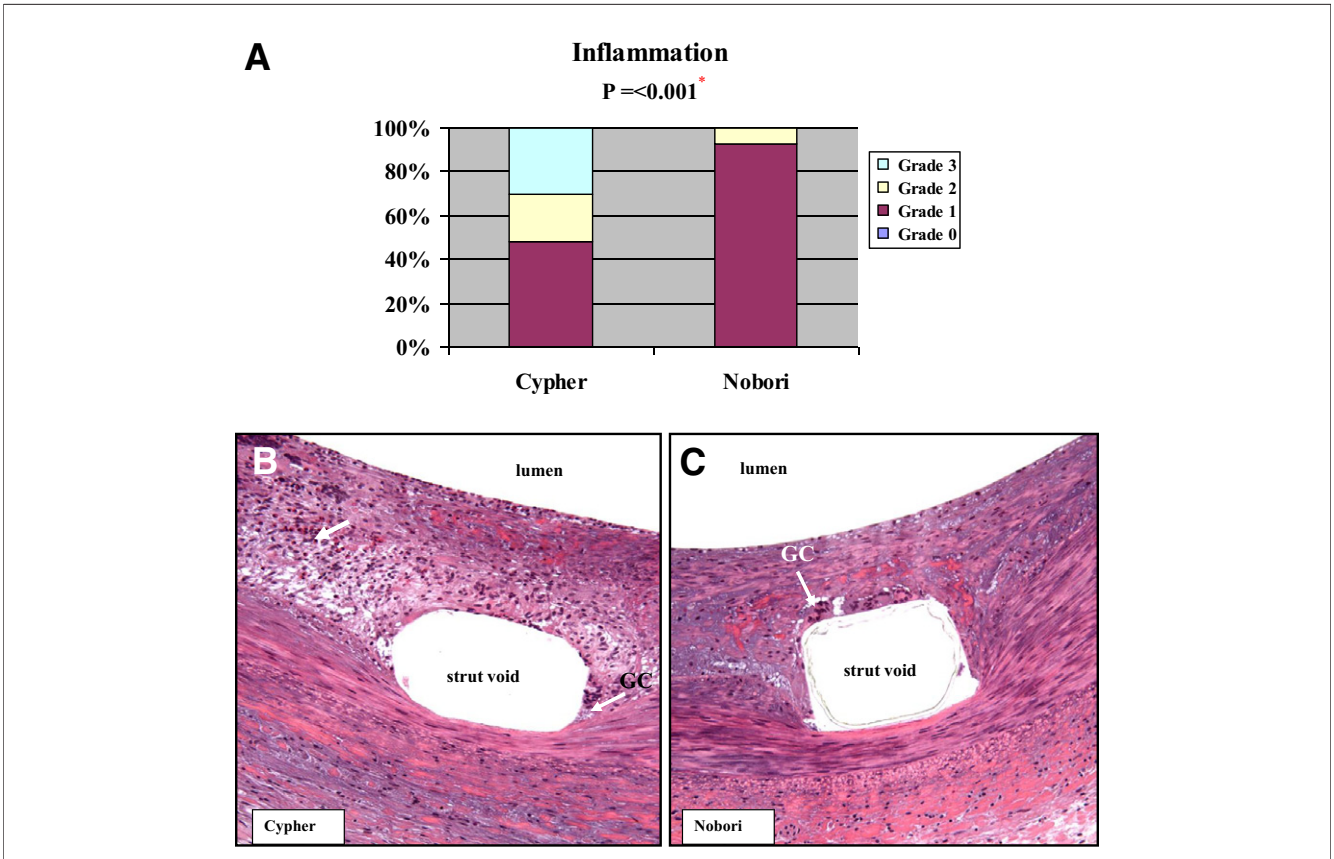

Figure 2. Histopathologic Scoring for Inflammation in Cypher and Nobori Groups

(A) The Nobori group showed significantly lower inflammation. High magnifications of (200×) of **(B)** Cypher and **(C)** Nobori hematoxylin-eosin–stained sections are shown. **White arrows** indicate the inflammatory cells. *Nobori group showed significantly lower inflammation than the Cypher group (p < 0.001). GC = giant cell.

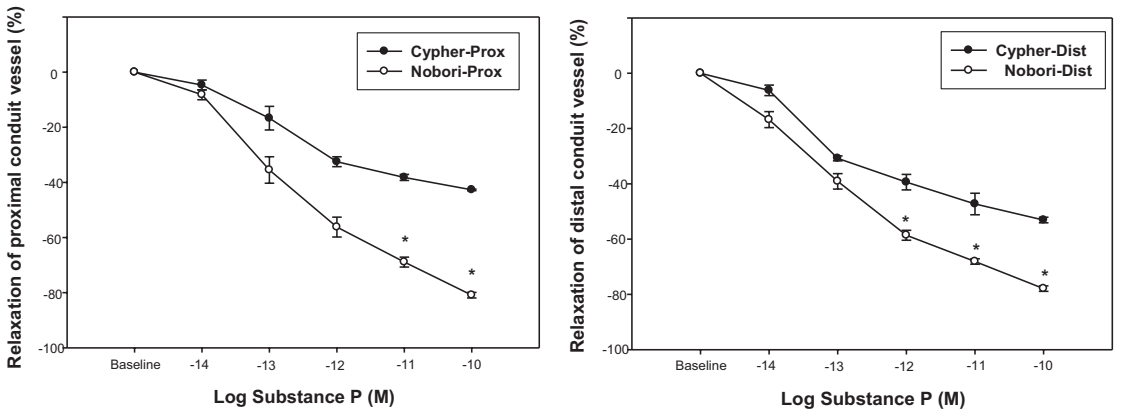

Figure 4. Relaxation Response to Substance P Proximal and Distal to Stent

The Nobori group showed significantly higher relaxation at maximal substance P concentration than the Cypher group did. *$p < 0.05$ Nobori versus Cypher. Abbreviations as in Figure 3.

lower superoxide production. Moreover, stented segments of Nobori also showed a lower inflammatory score. Similar to our current study findings, several clinical studies have shown long-term (6 to 9 months) vasomotor dysfunction involving the coronary segments proximal and/or distal to both sirolimus- and paclitaxel-eluting stents (10–13). At the same time, our results are somewhat in contrast to the results of a recent publication by van den Heuvel et al. (14) showing that in healthy porcine coronaries, sirolimus-eluting stents did not affect distal coronary vascular function, whereas paclitaxel-eluting stents altered distal endothelial function of small arteries under conditions of reduced NO bioavailability. There are significant differences in both studies, including the animal model, stent length, implantation technique, and the follow-up duration. To get a robust signal and to better understand the underlying mechanisms, we used much longer stents (28 vs. 13 mm) compared with those used by van den Heuvel et al. (14) that might be contributing to the differences in the observed results.

Delayed healing, hypersensitivity reaction to drug and/or polymer, insufficient re-endothelialization, or dysfunctional endothelium have been implicated in the development of stent thrombosis (5–7). Much of our basic understanding of the vascular responses (both anatomical and physiological) to DES has been generated from animal studies. Given the limited resolution of conventional angiography, intravascular ultrasound, or other newer imaging modalities, histological studies remain the most commonly used method for evaluating arterial responses to vascular stent implants (6).

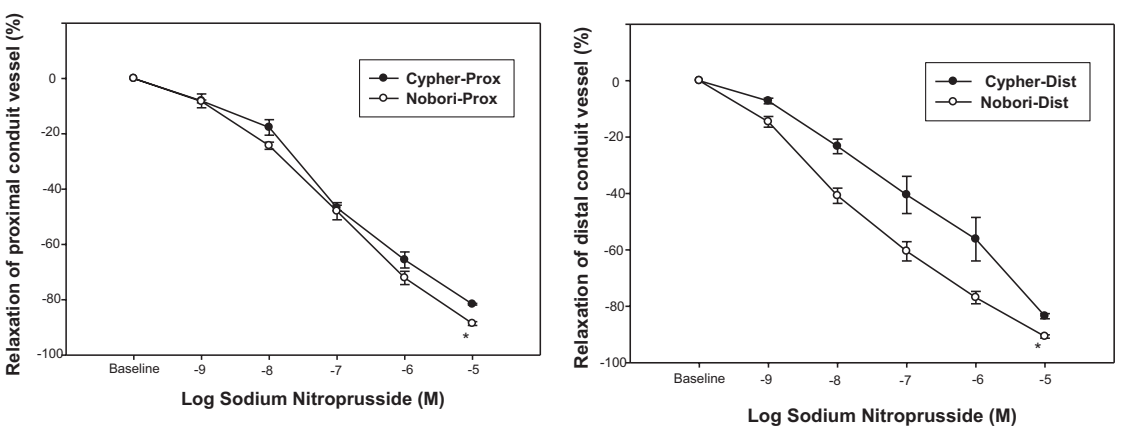

Figure 5. Relaxation Response to SNP Proximal and Distal to Stent

There was no difference between the Nobori and Cypher groups at 4 lower doses of sodium nitroprusside (SNP)-induce relaxation. However, the Nobori group demonstrated significantly greater relaxation to SNP at maximal dose than the Cypher group did. *$p < 0.05$ Nobori versus Cypher. Abbreviations as in Figure 3.

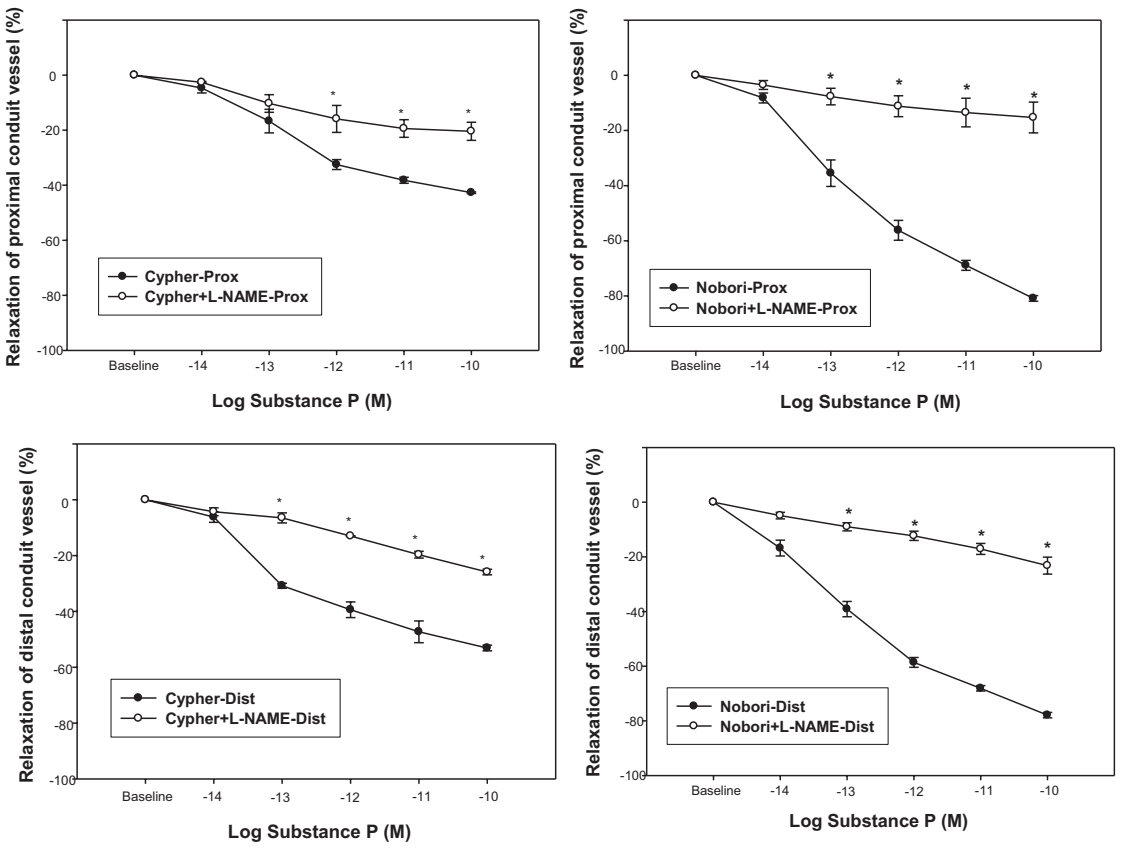

Figure 6. Relaxation Responses to Substance P Proximal and Distal to Stents with L-NAME

In the presence of N^G-nitro-L-arginine methyl ester (L-NAME), both the Cypher and Nobori groups' relaxations to substance P were significantly blocked in Prox and Dist segments. *$p < 0.05$, substance P versus substance P + L-NAME. Other abbreviations as in Figure 3.

Although arterial repair after stent placement in normal animals occur much more rapidly than in humans, the sequence and time line of biological responses share many similarities (15). In a swine model after BMS implantation, endothelial cell coverage is observed in approximately 40% of animals after 3 days, in about 80% after 7 days, and almost 100% after 14 days (6). In contrast to BMS, polymeric DES implantation in an animal model is noted to provoke progressive granulomatous and eosinophilic reactions starting around 28 days with continued increase up to 6 months (1 month, 14%; 3 months, 43%; and 6 months, 60%) (7). The likely explanation for these findings is a local hypersensitivity reaction to the nonerodible polymers incorporated into first-generation stents (Cypher: polyethylene-co-vinyl acetate and poly n-butyl methacrylate; Taxus: poly [styrene-b-isobutylene-b-styrene]). Although the eluted and retained drug may also contribute to these effects, the hypersensitivity reaction peaks only after complete release of drug in the pig model (i.e., >60 days), reinforcing the polymer as the more likely culprit. Tada et al. (16) recently reported granulomas in 10% of pigs at 28 days and 23.1% at 180 days after Cypher DES implantation. In contrast, neither high nor low doses of polymer-free biolimus A9 showed any granulomas during the same periods.

The Nobori stent that is used in this study has a bioresorbable polymer (polylactic acid) for biolimus A9 elution only on the abluminal surface, which provides a small initial burst and sustained simultaneous drug release and polymer degradation taking place over a period of more than 6 months (12). Interestingly, in our study, 1 Cypher stent and 1 Nobori stent were implanted in the same pig. At explantation, we noticed a severe hypersensitivity reaction with the Cypher stent but not with the Nobori stent. This observation suggests that the hypersensitivity response may be specific to the stent but not to the animal. Recently, Hamilos et al. (13) examined the effects of various drug-polymer devices on endothelium-dependent coronary vasomotion. Their study comparing the Cypher stent to the Nobori stent reported almost complete preservation of endothelium-dependent vasomotion in adjacent segments for the Nobori stent but not for the Cypher stent. The investigators concluded that first-

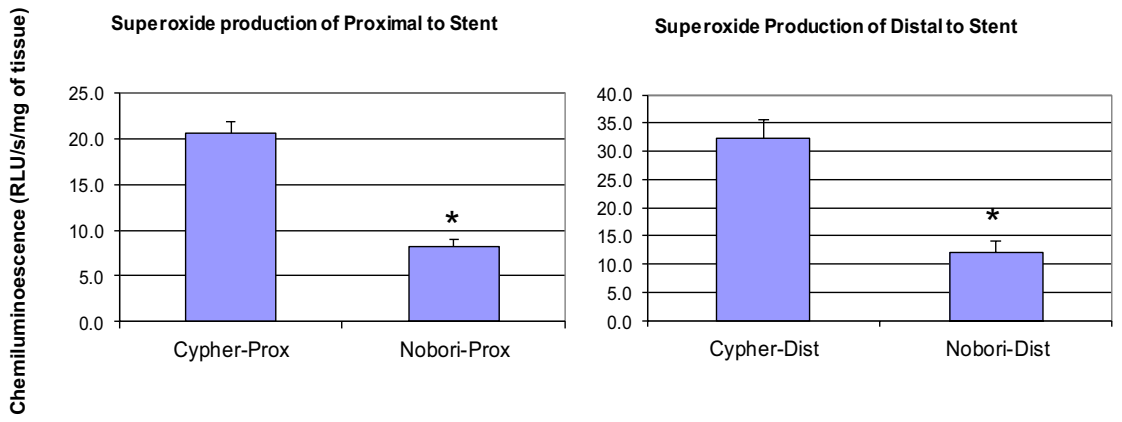

Figure 7. Superoxide Anion Production Proximal and Distal to Stent

Superoxide production measured by lucigenin chemiluminescence was significantly lower in the Nobori group than it was in the Cypher group. *$p < 0.01$, Nobori versus Cypher in proximal and distal segments. RLU = relative light units; other abbreviations as in Figure 3.

generation DES caused endothelial dysfunction in the implanted coronary vessels, whereas newer generation DES, such as Nobori, preserved normal endothelium-dependent vasomotion.

Molecular mechanisms of impairment of vascular endothelial function after DES implantation are not well understood. Multiple factors may be involved, including a direct toxic effect of the entrapped drug and/or an acute or delayed hypersensitivity reaction to the polymer. Long et al. (17), in a mice model, reported that acute in vitro sirolimus treatment, as well as genetic deletion of the sirolimus-receptor isoform FKBP12.6, increased protein kinase C-mediated endothelial NO synthase threonine 495 phosphorylation, thereby leading to decreased vascular NO production and subsequent endothelial dysfunction. Our studies have shown that superoxide production was significantly lower in the Nobori than in the Cypher group. Similar to our prior reported pre-clinical data with paclitaxel-eluting stents as well as with Cypher stents, persistent inflammation in the stented region contributes to increased free radical production. Oxygen free radical production depletes NO reserves, ultimately contributing to endothelial dysfunction (8).

Chronically increased production of reactive oxygen species leads to decreased NO bioavailability (secondarily to inactivation by $O_2^{\cdot-}$), resulting in impairment of endothelium-mediated vascular response. The importance of NO for endothelium-dependent relaxation was also confirmed in our experiment by significant blockage of vasorelaxation in the presence of NO synthase inhibited N^W-nitro-L-arginine methyl ester.

Thus, chronic inflammation, as well as potentiation of superoxide production, in the stented segment may contribute to endothelial dysfunction of the peristent segment. Beyond vasorelaxation dysfunction, our data also illustrated significantly increased contractile response to endothelin-1 in the Cypher group. The clinical implications and long-term significance of this endothelial dysfunction related to DES is currently unknown.

Study limitations. The study was limited to Cypher and Nobori DES and did not include BMS or stents coated with polymer only. Therefore, the potential interactive contributions of stent platform and polymer cannot be separated from the presence of drug. Additionally, our protocol did not include a bolus of clopidogrel, a recommended practice in clinical use. Because the DES were deployed in nondiseased porcine arteries, the results may not correspond to human atherosclerotic disease.

Conclusions

In this study, a novel DES (Nobori) was tested in pig coronary arteries and compared with Cypher DES. Vasomotor function, free radical production of vessel segments proximal and distal to the stent, and histological measurements of stented segments were performed. There was an increased endothelium-dependent relaxation, decreased endothelin-1 contraction, and lower superoxide production in the vessel segments proximal and distal to the stent, along with reduced inflammation of the stented segments in the Nobori group. Our study demonstrated that the Nobori stent, using a novel polymer and polymer-coating design elicited significantly lower inflammatory response and rapid recovery of endothelial function as compared to the Cypher DES.

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Key Words: biolimus A9-eluting stent(s) ■ coronary arteries ■ endothelial function ■ inflammation ■ oxidative stress.