Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 42, No. 8, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)01056-8

# Addition of Paclitaxel to Contrast Media Prevents Restenosis After Coronary Stent Implantation

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**OBJECTIVES** The present study was designed to test the efficacy of paclitaxel added to the contrast agent iopromide in the prevention of restenosis.

**BACKGROUND** Contrast media adhere to the coronary vessel wall for some seconds after injection. Such a layer of contrast agent could serve as a matrix for antiproliferative drugs.

**METHODS** Thirty-four stents were implanted into the left anterior descending and circumflex coronary arteries of 17 pigs, using a 1.2:1.0 overstretch ratio. The unsupplemented contrast agent iopromide-370 was used as a control; the treatment groups were treated with 80 ml intracoronary iopromide plus either 100 or 200 μmol/l paclitaxel, or 80 ml intravenous iopromide plus 200 μmol/l paclitaxel. Quantitative angiography and histomorphometry were used to assess comparable baseline parameters between the treatment groups.

**RESULTS** A short time incubation (3 min) almost completely inhibited vascular smooth muscle cell proliferation, sustained for up to 12 days. Whereas intravenous paclitaxel had no effect, intracoronary application of paclitaxel reduced the diameter stenosis from 55 ± 13% to 29 ± 18% and 13 ± 12%. Late lumen loss dropped from 1.94 ± 0.35 mm under the control condition to 1.19 ± 0.55 mm with 100 μmol/l paclitaxel and to 0.82 ± 0.54 mm with 200 μmol/l paclitaxel. Histomorphometry revealed a corresponding dose-dependent reduction of the neointimal area and restenosis by intracoronary iopromide paclitaxel. Assessment of left ventricular function and myocardial histology revealed no adverse effects of intracoronary paclitaxel application.

**CONCLUSIONS** This study provides evidence that intracoronary application of a taxane dissolved in a contrast medium profoundly inhibits in-stent restenosis. This novel, widely feasible approach may be suited for the prevention of restenosis in a broad spectrum of interventional treatment regimens. (J Am Coll Cardiol 2003;42:1415–20) © 2003 by the American College of Cardiology Foundation

Restenosis prevention continues to be a challenging task. Preclinical and clinical trials have shown that drug-eluting stents (DES) suppress neointimal proliferation (1,2). However, the efficacy and safety have not been ensured in all clinical settings, with remaining uncertainties in, for example, diabetics, acute coronary syndromes, bifurcation lesions, small vessels, or in-stent restenosis. Non–stent-based local delivery of antiproliferative drugs may offer additional flexibility and efficacy in the entire range of applications and may also affect vessel areas beyond the immediate stent coverage, which could be of special interest for small and tortuous vessels. Furthermore, healing and re-endothelialization of stent struts bare of antiproliferative agents may be facilitated.

Contrast agents delineate the contour of coronary arteries for some seconds after injection due to a low local flow velocity. We assume that such a layer of contrast agent adherent to the endothelium could provide a matrix for antiproliferative drugs. A key requirement for such a mode of drug delivery would have to be a rapid uptake by the vessel wall to achieve growth inhibition. Antiproliferative taxanes such as paclitaxel are highly lipophilic and bind tightly to cellular tissue (3), resulting in local retention at the site of delivery (4,5). The new approach of combining paclitaxel with a contrast agent is attractive because it does not require a particular delivery device or a specified stent.

The aim of the present study was to test the efficacy of different concentrations of paclitaxel added to the contrast agent iopromide for restenosis inhibition and to evaluate potential cardiotoxic effects of intracoronary administration.

## METHODS

**Study drugs.** The contrast agent iopromide-370 (Ultravist, Schering AG, Berlin, Germany) was used alone or as a solvent for paclitaxel in this investigation of cell culture experiments and in porcine coronary studies. Paclitaxel is widely used in antineoplastic chemotherapy (3).

For in vitro studies, iopromide-370 was diluted with water for injection to make a 40.5% vol/vol solution, which is isosmotic. Paclitaxel was dissolved in the contrast agent, which contained 1% vol/vol ethanol and was further diluted 1:1 with cell culture medium to a final taxane concentration of 1.46 μmol/l ("low concentration") or 14.6 μmol/l ("high concentration") in the incubation solution.

For the porcine efficacy studies, iopromide (Ultravist) was used in group I (control). Group II was injected with additional intravenous iopromide containing 200 μmol/l

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Manuscript received March 10, 2003; revised manuscript received June 5, 2003, accepted June 9, 2003.

**Abbreviations and Acronyms**

CM = contrast medium
Cx = circumflex artery
DES = drug-eluting stent
DMEM = Dulbecco's minimal essential medium
EEL = external elastic lamina
FBS = fetal bovine serum
LAD = left anterior descending coronary artery

paclitaxel at the same dose and time schedule as for the intracoronary contrast agent. Groups III and IV received intracoronary iopromide containing 100 and 200 μmol/l paclitaxel, respectively. In the tissue uptake study, 200 μmol/l paclitaxel in Ultravist-370 was used for coronary angiography. The dose was kept constant at 80 ml per animal, with the exception of group II, which received an additional 80 ml intravenously.

**Cell culture experiments.** Bovine aortic smooth muscle cells (passages 3 to 10) were cultured using Dulbecco's minimal essential medium (DMEM) supplemented with 10% fetal bovine serum (FBS). Cells were seeded at 10,000/$cm^2$ and incubated for 3, 10, or 60 min with 0.9% saline (control) and iopromide supplemented with paclitaxel. The supernatant was removed; cells were washed with 0.9% saline and cultured with DMEM plus 10% FBS. At days 0, 3, 6, 9, and 12, cell counts were assessed.

**Animal studies.** All experiments were conducted in accordance with the guidelines for animal experiments set forth by the local animal protection committee. Domestic pigs were presedated with an intramuscular injection of ketamine and xylazine. Venous access was provided and anesthesia initiated by intravenous injection of propofol, followed by orotracheal intubation, maintained with 1.0 to 2.0 vol% isoflurane, 70 vol% $N_2O$, and 30 vol% oxygen. All animals received 5,000 IU heparin, 250 mg aspirin intravenously (Aspisol, Bayer AG, Germany), and intracoronary nitroglycerin. The coronary arteries were imaged using a standard angiographic technique via the right carotid artery. Target segments were selected in the left anterior descending (LAD) and circumflex (Cx) coronary arteries.

**Paclitaxel concentration in tissue and plasma.** To determine the paclitaxel plasma level and uptake of paclitaxel into the vessel wall and various tissues, nine domestic pigs (26.4 ± 0.9 kg body weight) received stainless-steel stents into the LAD and Cx arteries (diameter 3.5 mm, length 13 mm; MultiLink Duet, Guidant, Germany) while injecting 80 ml iopromide containing 200 μmol/l paclitaxel as intermittent boluses. Blood samples were taken to determine the time course of systemic paclitaxel concentration. After 10 min, 2 h, and 24 h, stented segments, coronary artery segments 1.5 cm proximal and distal from the stented portion, and myocardial tissue about 5 mm apart from the LAD or Cx without major branches of the coronary arteries, respectively, were dissected. Additionally, three segments from the right coronary artery were studied. Paclitaxel was extracted from homogenized tissue samples by dimethyl sulfoxide and from plasma samples with docetaxel as an internal standard by ethyl acetate. Samples were analyzed by high-performance liquid chromatography using Waters Symmetry column C-18, 5 μmol/l, 25 cm × 4.6 mm, and acetonitrile/0.005 potassium phosphate buffer pH 3.5 (40:60, paclitaxel retention time 35 to 45 min; or 55:45, paclitaxel retention time ca 7.5 min), detection by ultraviolet photometry at 230 nm.

**Restenosis study.** Stainless-steel stents (diameter 3.0 to 3.5 mm, length 16 mm; FlexMaster, Jomed, Rangendingen, Germany) were implanted into the LAD and Cx arteries in 17 domestic pigs (weight 25.8 ± 1.5 kg). The animals were randomized to control (unsupplemented contrast agent iopromide-370), 80 ml intracoronary iopromide plus either 100 or 200 μmol/l paclitaxel, or 80 ml intravenous iopromide plus 200 μmol/l paclitaxel. The route of study drug administration was unblinded, but all data analyses were blinded.

Prophylactic intramuscular streptomycin and penicillin were given. Aspirin, 100 mg, and ticlopidine, 250 mg/day, were orally administered starting three days before the procedure and continued for 28 days. Follow-up angiography was performed 28 days later, and the animals were subsequently sacrificed using 3 mol/l KCl under deep anesthesia. Hearts were rapidly excised; the coronary system flushed with 0.9% saline; and the arteries fixed by perfusion with 4% buffered formalin under physiologic pressure and overnight immersion. The target vessel segments were then dissected, and samples for histologic analysis were obtained. Six samples of myocardium were taken: three from the left myocardium exposed to the selective contrast medium injections and three from the right heart. Histopathologic evaluation was performed by the Laboratory of Pharmacology and Toxicology KG (Hamburg, Germany).

Coronary imaging was done using a Philips PolyArc fluoroscope connected to a digitizer using an Apple Macintosh Power PC. The CAAS II System (Pie Medical, the Netherlands) was used for quantitative coronary analysis by two experienced cardiologists blinded to the treatment groups. Discrepancies were resolved by mutual consensus. Left ventricular levocardiography was used to evaluate measures of left ventricular function from the angiography at 28-day follow-up.

**Histologic analysis.** Stented coronary arteries were dissected from the formalin-fixed hearts and immersed in methylmethacrylate (Merck, Darmstadt, Germany). Three representative cross sections per stent were separated from the blocks with a coping saw, polished, and glued on acrylic plastic slides. Final specimens were stained by the van Gieson and hematoxylin-eosin technique. After digitalization, histomorphometric measurements were taken with the NIH image program (PC version "Scion Image," Scion Corp., Frederick, Maryland). The evaluated parameters were the lumen diameter, external elastic lamina (EEL) diameter, maximal neointimal thickness, EEL area, lumen

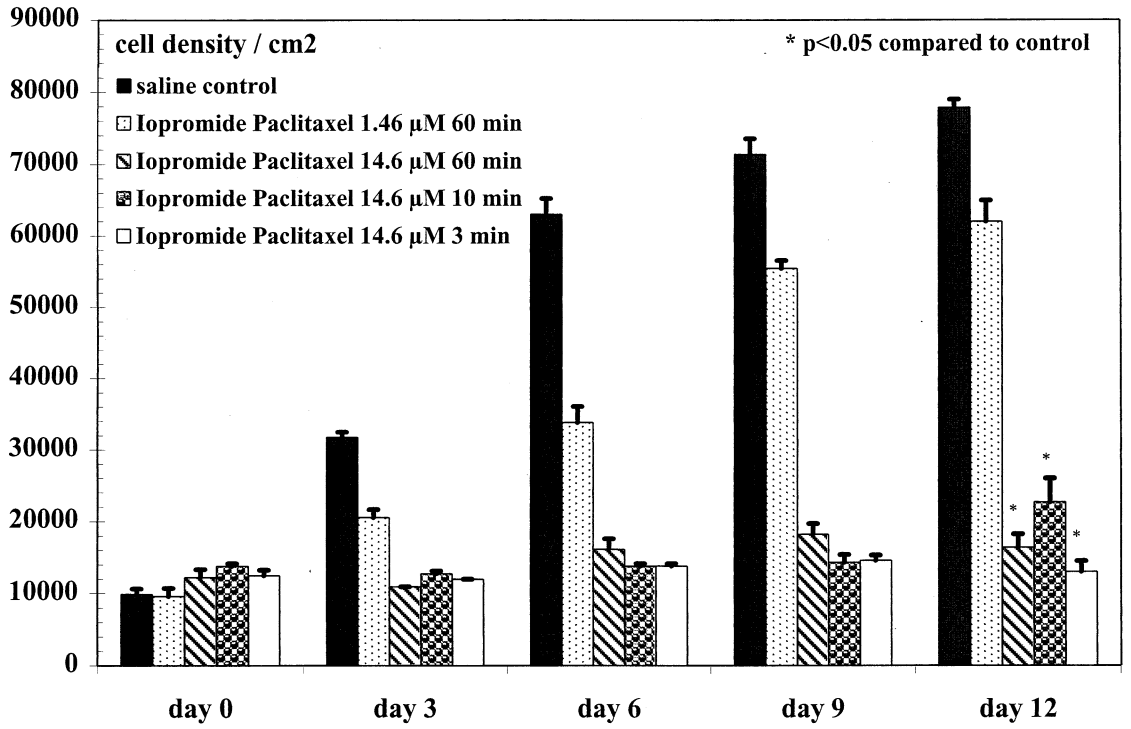


**Figure 1.** Effects of different concentrations and incubation times (60, 10, and 3 min) of iopromide (75 mg/ml iodine) or iopromide plus paclitaxel (1.46 or 14.6 μmol/l) as the final concentration in the cell culture medium. Bovine aortic smooth muscle cells (passages 3 to 10) were seeded at 10,000/cm$^2$, cultured with DMEM plus 10% FBS; cell counts were taken on days 0, 3, 6, 9 and 12. *$p < 0.05$ vs. control; $n = 50$.

area, and neointimal area. The injury score was assessed as previously described by Schwartz et al. (6).

**Statistical analysis.** Histomorphometric variables of the three cross-sectional planes were averaged to obtain a mean value per stent. Continuous variables of quantitative coronary angiography and histomorphometry were compared by analysis of variance (one-way repeated measures, 3 or 4 factors) using the software SPSS version 11.0 for Windows (SPSS Inc., Chicago, Illinois). Data are presented as the mean value ± SD.

## RESULTS

**Cell culture experiments.** Addition of paclitaxel (1.46 or 14.6 μmol/l) to iopromide for 3, 10, and 60 min to the cell culture medium significantly inhibited vascular smooth muscle cell proliferation in a concentration-dependent manner. Incubation times of 10 and 3 min with a concentration of 14.6 μmol/l paclitaxel exhibited the same efficacy as the 60-min incubation (Fig. 1).

**Intracoronary paclitaxel uptake.** Coronary artery segments of ~1.5 cm length were prepared 5 min, 2 h, and 24 h after catheterization to quantify the paclitaxel concentration, as depicted in Table 1. Initial concentrations measuring 10 to 15 μmol/l were comparable for all LAD segments (proximal, stented, distal; Table 1). Concentrations in the Cx segments were about half as high, whereas samples taken from the right coronary artery, which were not directly perfused by the contrast medium (CM)-paclitaxel preparation, reached about 1 μmol/l. Two hours after stent implantation, paclitaxel concentrations in the samples from the LAD and Cx were about 2 μmol/l. This indicates a half-life of paclitaxel in the LAD of about 45 min and in Cx of 85 min. Twenty-four hours after CM injection and stent implantation, paclitaxel was still detected in the LAD of two of three pigs, whereas it was below the detection limit of 0.4 μmol/l in half of the samples taken from the Cx. The paclitaxel concentration in plasma was 0.46 ± 0.22 μmol/l ($n = 9$) immediately following the last injection, decreasing to 0.074 ± 0.025 and 0.039 ± 0.018 μmol/l after 30 or 60 min, respectively ($n = 3$ each).

**Restenosis study.** In one pig, the interventional procedure was complicated by a flow-limiting dissecting, resulting in total occlusion of the Cx. The animal survived; however, it was excluded from further analysis. The remaining 16 pigs with 32 stents recovered and survived the follow-up period.

Baseline data were comparable between the treatment groups. Histologic analysis revealed sufficient stent expansion. The coronary artery sizes by the EEL diameter and area were similar in all groups. After 28 days, there were no significant angiographic or histomorphometric differences between group I (iopromide) and group II (intravenous application of iopromide paclitaxel). The intracoronary iopromide paclitaxel groups showed a marked reduction of the parameters characterizing in-stent restenosis, compared with the control group (Table 2, Fig. 2). When comparing the angiographic measurements by the parameters listed in

**Table 1.** Paclitaxel Concentration in 15-mm Segments of Coronary Arteries at Various Times After the Injection of 80 ml Iopromide-370 With 200 μmol/l Paclitaxel in the LAD and Cx of Nine Pigs

| | Paclitaxel Concentration | | | | | |
|---|---|---|---|---|---|---|
| | ~5 min After Last CM Injection | | 2 h After Last CM Injection | | 24 h After Last CM Injection | |
| | μmol/l | n | μmol/l | n | μmol/l | n |
| LAD | | | | | | |
| Stented segment | 12.2 ± 0.9 | 3 | 1.39 ± 0.35 | 3 | 0.67 ± 0.73 | 3 (1) |
| Proximal segment | 13.3 ± 3.1 | 3 | 2.73 ± 0.92 | 3 | 0.58 ± 0.52 | 3 (1) |
| Distal segment | 12.2 ± 1.2 | 3 | 2.73 ± 0.92 | 3 | 0.55 ± 0.52 | 3 (1) |
| Cx | | | | | | |
| Stented area | 5.5 ± 1.3 | 3 | 1.66 ± 0.24 | 3 | 0.57 ± 0.64 | 3 (1) |
| Proximal segment | 3.8 ± 0.4 | 3 | 2.02 ± 0.16 | 2 | 0.32 | 3 (2) |
| Distal segment | 9.1 ± 2.5 | 3 | 3.17 ± 0.78 | 3 | 0.21 | 3 (2) |
| Right coronary artery (untreated control) | 1.2 ± 1.4 | 8 | 1.06 ± 0.57 | 9 | 0.32 ± 0.60 | 9 (6) |

Data are presented as the mean value ± SD. Numbers in parentheses indicate the number of samples below the detection limit of <0.4 μmol/l. Extraction from homogenized tissue samples by DMSO; analyzed by HPLC. Concentrations below the detection limit were set at 0.00 μmol/l, and included in the calculation of mean values.

CM = contrast medium; Cx = circumflex artery; LAD = left anterior descending coronary artery.

Table 2, there was a significant reduction of restenosis. High-dose intracoronary iopromide paclitaxel led to a reduction of the neointimal area by 56% and maximal neointimal thickness by 62% (Table 3). Despite the marked reduction of neointimal proliferation, covering of stent struts with a thin layer of neointima was ensured in all samples.

**Myocardial tolerance.** After 28 days, there were no differences in parameters characterizing global and local left ventricular ejection fraction between the treatment groups. Histopathology did not reveal any treatment-related findings, but only incidental inflammatory reactions, vessel dilation, or perivascular edema in tissue samples from the left and right myocardium in all treatment groups.

## DISCUSSION

Coronary stents coated with antiproliferative agents such as sirolimus or paclitaxel have shown promising antirestenotic effects in clinical trials (2). However, antiproliferative effects are potentially restricted to the stented area, probably resulting in reduced protection of segments proximal and distal to the stent. Efficacy and safety have not been entirely defined in all possible clinical settings, especially in patients at increased risk of restenosis. Furthermore, concerns have been raised that such drug-releasing stents, while effective, may (similar to radiation) be prone to sudden thrombotic occlusion (7), delayed restenosis (8), or late malapposition (9). Polymeric matrixes on the stent embedding the antiproliferative drug itself could induce inflammation and thrombosis (10). Incomplete healing of stent struts may jeopardize the outcome (11).

Non–stent-based local delivery of antiproliferative drugs may offer additional flexibility in the range of applications and may access vessel areas outside the immediate coverage of stents. Because stent struts are not the direct source of the drug, healing may be facilitated.

The new concept using contrast media as a matrix for antiproliferative drugs simply employs standard coronary angiography. The hydrophobic paclitaxel exerts preferential tissue binding, allowing for effective convection and diffu-

**Table 2.** Results of Quantitative Coronary Angiography

| | Iopromide (n = 10) | Intravenous Iopromide Paclitaxel 200 μmol/l (n = 10) | Intracoronary Iopromide Paclitaxel 100 μmol/l (n = 10) | Intracoronary Iopromide Paclitaxel 200 μmol/l (n = 10) | p Value |
|---|---|---|---|---|---|
| Baseline angiography | | | | | |
| Reference diameter (mm) | 2.59 ± 0.22 | 2.83 ± 0.19 | 2.54 ± 0.25 | 2.65 ± 0.29 | 0.141 |
| Stent diameter (mm) | 3.19 ± 0.11 | 3.40 ± 0.10 | 3.15 ± 0.23 | 3.25 ± 0.19 | 0.039 |
| Overstretch ratio | 1.24 ± 0.08 | 1.21 ± 0.08 | 1.23 ± 0.09 | 1.25 ± 0.09 | 0.865 |
| 28-Day follow-up angiography | | | | | |
| Minimal lumen diameter (mm) | 1.26 ± 0.29 | 1.16 ± 0.37 | 1.96 ± 0.61 | 2.40 ± 0.40 | 0.001 |
| Diameter stenosis (%) | 55 ± 13 | 59 ± 12 | 29 ± 18 | 13 ± 12 | 0.001 |
| Late loss (mm) | 1.94 ± 0.34 | 2.25 ± 0.35 | 1.19 ± 0.55 | 0.82 ± 0.54 | 0.001 |

Reference diameter, stent diameter, and overstretch ratio (stent diameter/reference diameter) at baseline angiography. Minimal lumen diameter, diameter stenosis, and late lumen loss (stent diameter at baseline − minimal lumen diameter at control) after 28-day angiography. Data are presented as the mean value ± SD.

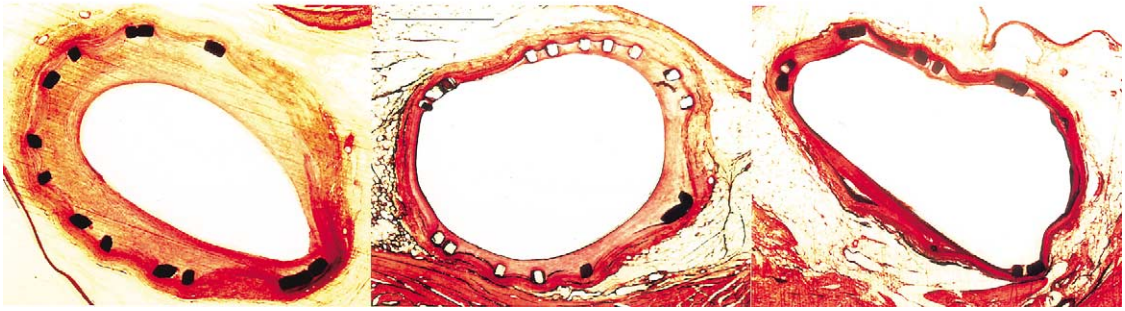

**Figure 2.** Histologic analysis of stented porcine coronary arteries after 28 days. Control **(left)**, 100 μmol/l intracoronary iopromide paclitaxel **(middle)**, and 200 μmol/l intracoronary iopromide paclitaxel **(right)**. Stented coronary arteries were dissected from the formalin-fixed hearts, immersed in methylmethacrylate, and separated from the blocks with a coping saw, polished, and glued on acrylic plastic slides. Specimens were stained by the hematoxylin-eosin technique.

sion into the arterial wall (4,12). However, competitive binding (e.g., by albumin and other plasma proteins) hampers paclitaxel accumulation (12). Therefore, plasma concentrations of paclitaxel sufficient to inhibit restenosis in the peripheral circulation would probably reach toxic levels (13).

The presented in vitro experiments indicate that short contact times with iopromide paclitaxel induce an almost complete inhibition of vascular smooth muscle cell proliferation. This is in agreement with our in vivo data showing direct pharmacokinetic evidence for uptake of the active compound in the vessel wall of opacified arteries and adjacent tissue at concentrations in the range of 3 to 15 μmol/l, which are similar to those effective in cell culture experiments. Vessel segments proximal and distal to the stented area were treated with concentrations identical to those of the vessel covered by the stent. Consequently, based on the long-lasting action of paclitaxel on cell growth and the fast uptake of the compound in the vessel wall, restenosis development was prevented. Notably, inhibition of neointimal growth is comparable to that achieved with DES (1,8).

Functional and histologic analysis excluded adverse effects on the myocardium. In the clinical setting, application of 60 to 100 ml contrast agent containing 100 to 200 μmol/l paclitaxel would translate into a total dosage of 5 to 17 mg paclitaxel per patient. This resembles only 2% to 6% of a single dose applied in tumor therapy, although the initial intracoronary taxane concentration during bolus application is substantially higher than plasma levels during cancer therapy (3). Plasma concentrations in pigs reached about one-tenth the concentrations measured in patients during tumor therapy lasting for a very short time.

**Conclusions.** This novel non–stent-based but vessel wall–directed treatment regimen, applying paclitaxel in contrast media, could be an efficacious, nonexpensive, and facile strategy to prevent restenosis.

## Acknowledgments

We thank Dr. Dirk Mahnkopf and his team from the Institute of Medical Technology, Magdeburg, Germany, for their excellent support in conducting the animal experiments, as well as Anakat GmbH, Berlin, Germany, for paclitaxel analysis. We thank Nicole Karthein for excellent assistance in cell culture experiments. We also thank JOMED GmbH, Rangendingen, Germany, for the contribution of medical devices.

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**Table 3.** Histomorphometry of Stented Porcine Coronary Arteries After 28 Days

| | | Iopromide Paclitaxel | | |
|---|---|---|---|---|
| | Control | ic 100 μmol/l | ic 200 μmol/l | p |
| n | 16 | 10 | 6 | |
| Injury score | 0.87 ± 0.12 | 0.88 ± 0.15 | 0.92 ± 0.07 | 0.723 |
| EEL area ($mm^2$) | 6.03 ± 1.37 | 6.14 ± 0.81 | 5.51 ± 0.19 | 0.516 |
| Luminal area ($mm^2$) | 2.33 ± 0.76 | 2.94 ± 1.11 | 3.78 ± 0.44 | 0.004 |
| Area stenosis (%) | 59 ± 13 | 51 ± 17 | 31 ± 10 | 0.001 |
| Neointimal area ($mm^2$) | 3.69 ± 1.38 | 3.19 ± 1.17 | 1.73 ± 0.62 | 0.008 |
| Maximal neointimal thickness (mm) | 0.77 ± 0.39 | 0.50 ± 0.23 | 0.29 ± 0.24 | 0.011 |

Injury score, external elastic lamina (EEL) area, luminal area, area stenosis, neointimal area, and maximal neointimal thickness. Histomorphometric measurements of the three cross-sectional planes were averaged to obtain a mean value per stent.

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