

Paclitaxel Stent Coating Inhibits Neointimal Hyperplasia at 4 Weeks in a Porcine Model of Coronary Restenosis

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Background—Despite limiting elastic recoil and late vascular remodeling after angioplasty, coronary stents remain vulnerable to restenosis, caused primarily by neointimal hyperplasia. Paclitaxel, a microtubule-stabilizing drug, has been shown to inhibit vascular smooth muscle cell migration and proliferation contributing to neointimal hyperplasia. We tested whether paclitaxel-coated coronary stents are effective at preventing neointimal proliferation in a porcine model of restenosis.

Methods and Results—Palmaz-Schatz stents were dip-coated with paclitaxel (0, 0.2, 15, or 187 $\mu\text{g}/\text{stent}$) by immersion in ethanolic paclitaxel and evaporation of the solvent. Stents were deployed with mild oversizing in the left anterior descending coronary artery (LAD) of 41 minipigs. The treatment effect was assessed 4 weeks after stent implantation. The angiographic late loss index (mean luminal diameter) decreased with increasing paclitaxel dose ($P < 0.0028$ by ANOVA), declining by 84.3% (from 0.352 to 0.055, $P < 0.05$) at the highest level tested (187 $\mu\text{g}/\text{stent}$ versus control). Accompanying this change, the neointimal area decreased (by 39.5%, high-dose versus control; $P < 0.05$) with increasing dose ($P < 0.040$ by ANOVA), whereas the luminal area increased (by 90.4%, high-dose versus control; $P < 0.05$) with escalating dose ($P < 0.0004$ by ANOVA). Inflammatory cells were seen infrequently, and there were no cases of aneurysm or thrombosis.

Conclusions—Paclitaxel-coated coronary stents produced a significant dose-dependent inhibition of neointimal hyperplasia and luminal encroachment in the pig LAD 28 days after implantation; later effects require further study. These results demonstrate the potential therapeutic benefit of paclitaxel-coated coronary stents in the prevention and treatment of human coronary restenosis. (*Circulation*. 2001;103:2289-2295.)

Key Words: paclitaxel ■ stents ■ angioplasty ■ restenosis

Restenosis remains a frequent cause of late failure after initially successful coronary angioplasty.¹ Coronary stents reduce restenosis by limiting the extent of elastic recoil and late vascular remodeling.² Despite these improvements, the incidence of restenosis remains high because of neointimal hyperplasia, which is induced by all forms of dilating mechanical injury and is aggravated by the presence of the stent (“in-stent restenosis”).³ Combining the mechanical support of a stent with a treatment to limit neointimal ingrowth should further improve therapeutic outcomes. This combined approach has been used successfully in intracoronary brachytherapy.^{4,5} Late thrombosis and edge stenosis (the “candy wrapper effect”) are potential complications that may limit the effectiveness of this approach.^{5,6}

Pharmacological inhibitors of neointimal hyperplasia, like paclitaxel, represent an alternative to radiation therapy.^{7,8} Paclitaxel (Taxol) is a derivatized diterpenoid that exerts an antineoplastic effect by interfering with cell microtubule function.^{9,10} Paclitaxel alters the dynamic equilibrium between microtubules and α - and β -tubulin by favoring the formation of abnormally stable microtubules.¹¹ This leads to the inhibition of cell division and migration, intracellular signaling, and protein secretion, which all rely on the rapid and efficient depolymerization of microtubules. Systemic application of paclitaxel in the rat showed that a significant (70%) reduction in neointimal proliferation could be achieved at blood concentrations 100 times lower than antineoplastic levels.⁷ In rat⁷ and human⁸ cultured cell models, paclitaxel

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prevented growth factor-stimulated vascular smooth muscle cell migration and proliferation, consistent with its effects on neointimal formation in vivo. As an alternative to systemic therapy, local drug delivery offers the advantages of allowing high local concentrations of drug at the treatment site while minimizing systemic toxic effects. For paclitaxel, local delivery might be achieved by a drug-delivery catheter⁸ or by a coated stent.¹²

The sustained delivery of paclitaxel to the arterial wall can be achieved with polymeric stent coatings, but these coatings may induce inflammation and thrombosis.¹² After an initial failed attempt with polymer-coated stents, we resorted to dip-coating metallic stents with paclitaxel dissolved in a volatile solvent (ethanol). Evaporation of the solvent leaves a fine residue of paclitaxel that adheres to the surface of the stent. By limitation of the coating to paclitaxel, the undesirable complications associated with certain polymers were avoided. The dip-coating technique also allows paclitaxel to have immediate contact with the vessel wall, favoring its rapid accumulation by arterial tissue. This strategy for local drug delivery resembles short-term irradiation⁴ by optimizing the conditions for blocking the earliest cellular events triggered by injury.^{13,14}

Methods

Stent Preparation

Palmaz-Schatz stents (Johnson & Johnson) were coated by dipping the stent into ethanolic paclitaxel and evaporating the solvent. This procedure left a fine residue of paclitaxel covering the surface of the stent. Results of local extravascular paclitaxel delivery studies in the rat (10 μg paclitaxel effectively inhibited neointimal growth; unpublished results) were used to establish 4 treatment groups: control (0 $\mu\text{g}/\text{stent}$), low-dose (0.2 $\mu\text{g}/\text{stent}$), intermediate-dose (15 $\mu\text{g}/\text{stent}$), and high-dose (187 $\mu\text{g}/\text{stent}$). Coated stents were checked for the uniformity of drug application by selecting several stents at random from each batch, extracting them in ethanol, and measuring paclitaxel by high-performance liquid chromatography (HPLC; Gilson). Paclitaxel was eluted from a 25-cm \times 4.6-mm pentafluorophenyl column (ES Industries) in a mobile phase consisting of 45% acetonitrile and 55% water flowing at 1.5 mL/min and monitored at 227 nm with a UV detector (Gilson model 116). Paclitaxel-coated stents were mounted on 3.0-mm balloons (PS1530 balloon delivery catheter; Johnson & Johnson) with a manufacturer-supplied crimping tool. Sterilization was carried out with ethylene oxide gas. Drug losses associated with the mounting and crimping procedure were evaluated by extracting the demounted stents in ethanol and subjecting the extract to HPLC. Loss of paclitaxel to the blood was determined by incubating paclitaxel-coated stents at 37°C in pig whole blood treated with 1 mmol/L EDTA to prevent clotting. The incubation time was varied to establish a paclitaxel washout curve.

Stent Deployment

All animal protocols were approved by the animal care and use committees of the National Institute on Aging, NIH, and Johns Hopkins University and were conducted according to established guidelines for the humane use and treatment of laboratory animals. Male and female NIH minipigs (n=43) weighing 35 to 45 kg were pretreated with aspirin (325 mg) and diltiazem (Cardizem CD; 180 mg) the day before stent implantation. Aspirin (325 mg) was given daily throughout the evaluation period. The animals were sedated with ketamine (20 mg/kg IM) and acetylpromazine (0.22 mg/kg IM) and given sodium pentobarbital (4 mg/kg IV) to facilitate supine positioning and endotracheal intubation. Anesthesia was maintained with 1% to 2% isoflurane in oxygen flowing at 2 L/min. An 8F

surgical technique, and heparin (5000 U) was administered as an intra-arterial bolus. The stent was delivered to the left anterior descending coronary artery (LAD) through an 8F Judkins right guiding catheter and deployed by two 30-second balloon inflations at 8 atm. The segment of artery to be stented was selected to allow \approx 1.2 times oversizing by visual estimation. Angulated and branching segments were stented if necessary to permit this degree of oversizing. Stent implantation was done by a single pair of operators (A.W.H. and M.W.) who were blinded to the treatment groups. Coronary angiography was performed in 2 views (generally antero-posterior and 30° left anterior oblique) immediately before and after stent implantation.

Angiographic Analysis

Angiograms were performed during the initial catheterization and at 4-week follow-up. The angiographic mean luminal diameter (MLD) within the stented segment was measured by computerized coronary angiography (ImageComm) by 2 blinded investigators (A.W.H. and B.S.A.). Two views were measured and averaged for each arterial segment. Neointimal encroachment of the lumen was evaluated from the late loss index (LLI), defined as $LLI = (MLD_0 - MLD_{4\text{wks}}) / MLD_0$, where MLD_0 and $MLD_{4\text{wks}}$ are the MLDs immediately after stenting and at follow-up, respectively.

Histological Preparation and Histomorphometric Analysis

After the terminal angiogram, the heart was excised and perfusion-fixed with 10% formalin at 100 mm Hg for 15 minutes. After overnight immersion-fixation, a segment of the LAD containing the stent was dissected from the myocardium. The LAD segment was embedded in acrylic plastic and cut into 3 blocks containing the proximal, middle, and distal portions of the stent. Three cross sections were cut from each of these blocks with a tungsten carbide knife and stained with elastic van Gieson or Movat pentachrome. Arterial tissue from adjacent (proximal and distal), nonstented segments of the LAD were paraffin-embedded and stained with the above dyes or hematoxylin and eosin. Histomorphometric analysis of the tissue sections was performed by computerized video imaging with an Axioplan microscope (Zeiss) and a black-and-white MTI video camera (Dage-MTI Inc). Video images were analyzed with IBAS 2.0 software (IBAS, Kontron Elektronik). The vessel injury score was determined by the method of Schwartz et al.¹⁵ The luminal and neointimal areas were evaluated for each of the tissue cross sections, averaged, and expressed as the absolute area in square millimeters. The neointimal and medial wall thicknesses (in millimeters) were measured halfway between each pair of strut openings (in-between distance) and averaged over all tissue cross sections. Neointimal thickness was also measured at each strut site (strut-lumen distance). All morphometric analyses were made by investigators (L.C. and C.N.) blinded to the treatment groups.

Determination of Postdeployment Paclitaxel Levels

Palmaz-Schatz stents dip-coated at the intermediate (16 $\mu\text{g}/\text{stent}$) and high (177 $\mu\text{g}/\text{stent}$) paclitaxel doses were deployed in the LAD and left in place for 10 to 15 minutes. The heart was removed and perfused with 10% formalin before dissection of the stented arterial segment to preserve the tissue architecture and minimize drug losses. The excised stent and surrounding segment of LAD were each extracted with 1 mL of absolute ethanol for 72 hours at room temperature. Paclitaxel in the ethanol extracts was determined quantitatively by HPLC.

Statistical Analysis

Angiographic and histological data were analyzed by comparing control and paclitaxel-coated stents by use of a 1-way ANOVA. Pairwise comparisons involving the control and different treatment groups were performed according to the post hoc Dunnett test, which corrects for multiple comparisons. The level of significance was taken as $P < 0.05$. Results are reported as mean \pm SEM.

TABLE 1. Stent Oversize Ratio, Vascular Injury Score, and Stent Circumference

Paclitaxel, $\mu\text{g}/\text{Stent}$	Oversize Ratio	Injury Score	Stent Circumference, mm
0	1.28 \pm 0.03	1.07 \pm 0.09	7.69 \pm 0.16
0.2	1.23 \pm 0.02	1.27 \pm 0.21	7.69 \pm 0.26
15	1.24 \pm 0.02	1.28 \pm 0.13	7.72 \pm 0.48
187	1.29 \pm 0.07	1.11 \pm 0.23	7.45 \pm 0.11

Oversize ratio indicates MLD after stenting/MLD before stenting; stent circumference, the linear distance from strut to strut around the circumference of the stent. Results are reported as mean \pm SEM.

Results

Forty-three pigs underwent stent placement in the LAD with paclitaxel-coated Palmaz-Schatz stents. All pigs survived to completion of the 4-week study without evidence of myocardial infarction on gross inspection. Forty-one pigs in 4 treatment groups were analyzed: 11 in the control (0 $\mu\text{g}/\text{stent}$), 8 at the low dose (0.2 $\mu\text{g}/\text{stent}$), 15 at the intermediate dose (15 $\mu\text{g}/\text{stent}$), and 7 at the high dose (187 $\mu\text{g}/\text{stent}$). Because efficacy was judged by the ability to inhibit neointimal hyperplasia induced by injury, animals with low injury scores and incomplete engagement of the stent struts were eliminated from further analysis. This occurred in 2 pigs in the control group with injury scores of 0.17 and 0.21; the mean injury score for the remaining 41 animals was 1.19 \pm 0.08 (mean \pm SEM). Uniformity of the applied injury was evident from the similarity in oversize ratios (1.26 \pm 0.02; P <0.231 by ANOVA) and injury scores (P <0.755 by ANOVA), which were not significantly different in the 4 treatment groups (Table 1).

Angiographic Analysis

The 4-week follow-up angiograms (Figure 1) showed a graded effect of paclitaxel dose, with the largest reduction in neointimal encroachment at the high dose. In the control angiogram, a distinctive narrowing of the stented LAD segment was evident that was less severe at the intermediate dose. At the high dose, a step-down in the luminal diameter occurred between the stented and nonstented segments, indicating effective inhibition of neointimal growth and/or mild arterial dilatation in the drug-applied region. No hyperplastic edge effects or aneurysmal

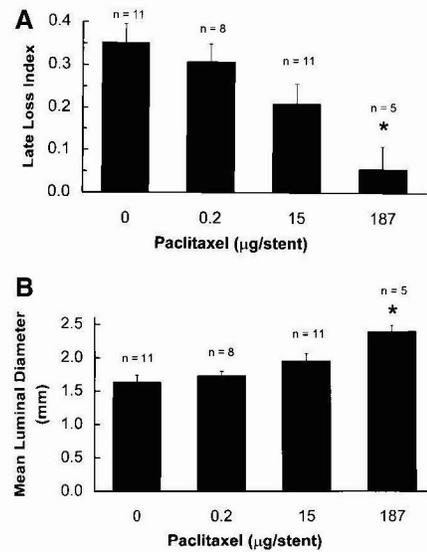


Figure 2. A, LLI vs paclitaxel dose. B, MLD at 4-week follow-up vs paclitaxel dose. Results are reported as mean \pm SEM. * P <0.05 vs control (Dunnett’s test).

dilatations were found in any of the treatment groups. Angiograms were evaluated for the MLD and LLI during the 4-week period (Figure 2). Application of ANOVA to the LLI data revealed that the difference between the treatment groups was significant (P <0.0028). The LLI was dose-dependent; between the control and high paclitaxel doses, the LLI fell from 0.352 to 0.055, declining by 84% (P <0.05 by Dunnett’s test). The change in MLD with increasing drug dose was inversely related to the decline in LLI. The gain in MLD rose to 146% of the control group at the high paclitaxel dose (P <0.05 by Dunnett’s test) and was highly significant across all group comparisons (P <0.0012 by ANOVA).

Histomorphometric Analysis

Representative arterial cross sections from the different treatment groups are shown in Figure 3. In the control (Figure 3A) and low-dose (Figure 3B) groups, the stent strut sites were clearly visible between the neointima and internal elastic lamina, causing mild compression of the medial wall. A progressive decline in the extent of neointimal formation was observed with

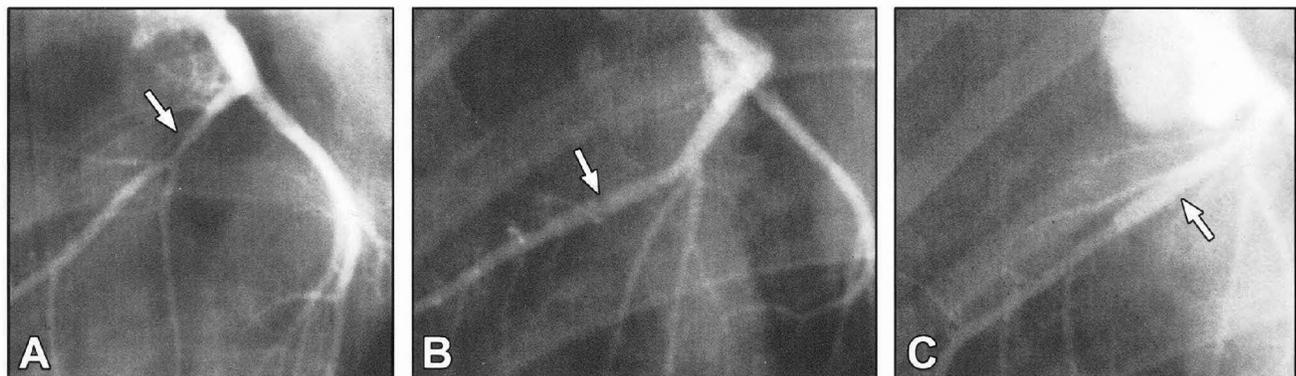


Figure 1. Four-week follow-up angiograms of stented LADs. A, No paclitaxel (control); B, intermediate-dose paclitaxel (15 $\mu\text{g}/\text{stent}$); and C, high dose paclitaxel (187 $\mu\text{g}/\text{stent}$). Arrows show approximate midpoint of stent.

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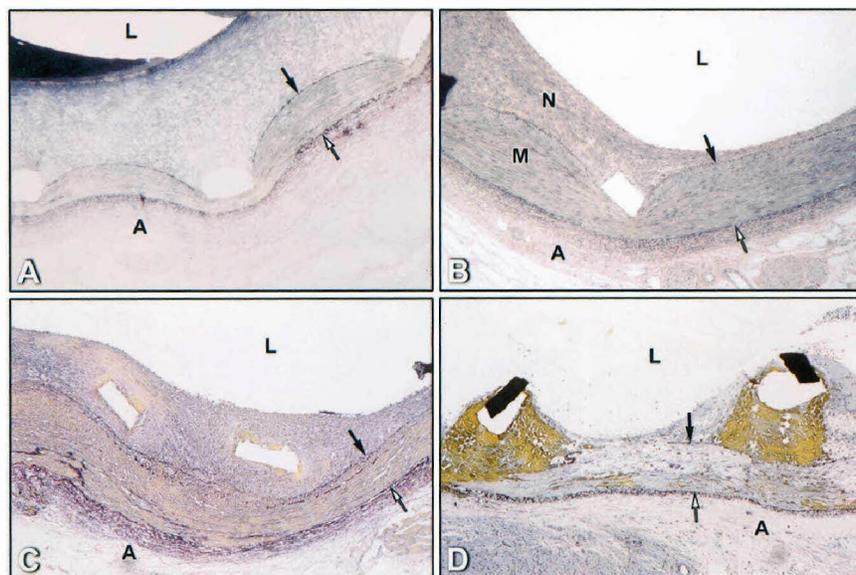


Figure 3. Photomicrographs of stented LAD cross sections (magnification $\times 40$). A, No paclitaxel (control); B, low-dose paclitaxel ($0.2 \mu\text{g}/\text{stent}$); C, intermediate-dose paclitaxel ($15 \mu\text{g}/\text{stent}$); and D, high-dose paclitaxel ($187 \mu\text{g}/\text{stent}$). Black material partially filling lumen in A is barium gelatin dye contrast medium. Solid and open arrows indicate boundaries formed by internal and external elastic laminae, respectively. L indicates lumen; N, neointima; M, tunica media; and A, tunica adventitia.

increasing drug dose. This inhibition was particularly evident at the high dose (Figure 3D), where the strut sites protruded into the lumen attached to the vessel wall by a narrow pedestal of acellular material. Expansion of the stent would have initially forced the struts into the medial wall like the control group, suggesting that these changes involved expansion of the vessel wall (ectasia or dilatation). Incomplete deployment of the stent as the cause of this effect was ruled out by the similarity in oversize ratios, injury scores, and stent circumferences (Table 1). Illumination of the acellular material with polarized light revealed that it was noncrystalline, which excluded paclitaxel or a metabolite as its probable source. Similar, less intensely stained deposits were seen surrounding the strut sites at the lower doses (Figure 3C) but were completely absent from the control group. Other histological changes (Table 2) included medial wall cell necrosis with associated calcified deposits and focal neointimal

and medial wall hemorrhage. The frequency of these changes increased with the applied drug dose, implicating paclitaxel in their origin. Infiltration of cells with inflammatory morphology was seen infrequently in the cross sections and was not correlated with the paclitaxel dose. A small number of sections showed a perivascular inflammation that was probably injury-related. The identification of endothelial cells was limited by the tissue processing technique; however, endothelium-like cells were occasionally seen surrounding the lumen, forming an incomplete barrier, in all of the treatment groups.

Figure 4A shows the dose-dependence of the neointimal area calibrated to the drug dose applied to the stent. Consistent with the relationship found in the LLI, the high-dose treatment group showed a significant reduction of neointimal formation compared with controls (39%; $P < 0.05$ by Dunnett's test); the significance with all group comparisons included was $P < 0.0402$ by ANOVA. A similar dose-dependence was observed in the neointimal thickness index (Figure 4C). Neointimal thickness declined significantly between the control and high-dose groups (55% in-between and 75% strut-lumen; $P < 0.05$ by Dunnett's test) and was significant over all groups ($P < 0.0058$ in-between and $P < 0.0001$ strut-lumen by ANOVA). As shown in Figure 4D, medial wall thickness was also reduced by 26% at the high drug dose compared with the control group ($P < 0.05$ by Dunnett's test). The decrease in medial wall thickness was not significant by ANOVA ($P < 0.09$), however, suggesting that the medial wall cells may be less sensitive to paclitaxel than those found in the neointima.

The change in luminal area with increasing drug dose was inversely related to the decline in the LLI and neointimal area (Figure 4B). The luminal area at the high dose was 190% of that for the control group ($P < 0.05$ by Dunnett's test), and the difference in luminal area was highly significant across all group comparisons ($P < 0.0004$ by ANOVA). An unintentional bias in oversizing the stent was ruled out on the grounds that the mean stent circumference, determined by summation of the strut-to-strut distances, was not significantly different in the 4 treatment groups (Table 1).

TABLE 2. Paclitaxel Histopathology

Tissue Event	Paclitaxel Dose, $\mu\text{g}/\text{Stent}$			
	0	0.2	15	187
Focal hemorrhage, %				
Neointima	<1	9	18	25
Medial wall	ND	ND	6	28
Tissue necrosis	ND	ND	2	13
Amorphous deposits, %				
Neointima	ND	<1	31	68
Medial wall	ND	ND	6	53
Inflammation, %	0.3	0.7	3.0	ND
Thrombosis, %	ND	ND	ND	ND

The arterial cross section was divided into N pie-shaped sectors, where N is the total number of stent struts. The frequency of a histopathological event was $(n \times 100)/N$, where n is the number of sectors in which the event appeared. For each pig, an average score was computed from the proximal, middle, and distal arterial cross sections. Data acquired from all pigs were used to compute the average score at a given dose. ND indicates not detectable. The presence of inflammation was detected as anything more than a very mild, noncircumferential infiltrate around the strut.

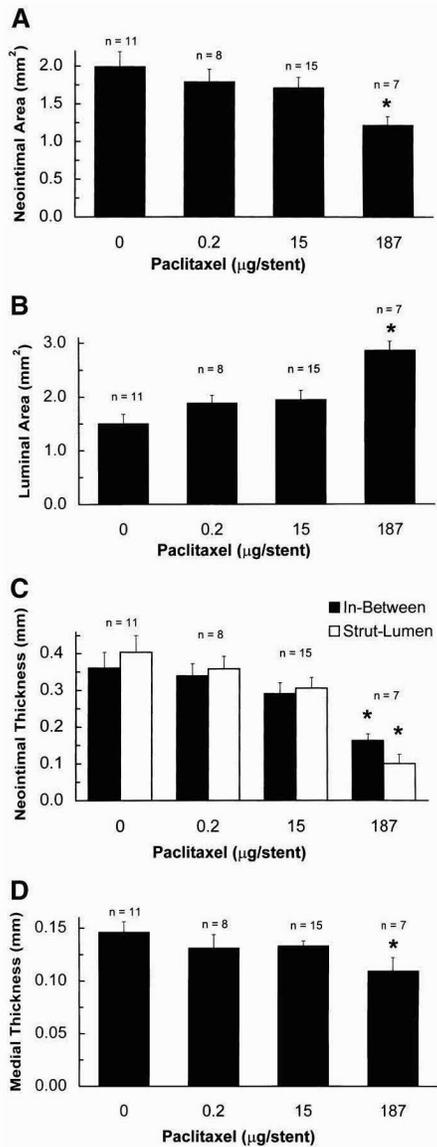


Figure 4. Dose-dependence of (A) neointimal area, (B) luminal area, (C) neointimal thickness, and (D) medial wall thickness. Neointimal thickness (in mm) was measured as linear distance from lumen to (1) stent strut site (strut-lumen) or (2) a point halfway between each pair of stent strut sites (in-between). Results are reported as mean±SEM. **P*<0.05 vs control (Dunnett's test).

Postdeployment Paclitaxel Levels

Short-term studies to determine the postdeployment paclitaxel levels (Table 3) showed that at the high paclitaxel dose, ≈68% of the drug originally deposited on the stent was recovered. Of this, slightly less than 50% of the dose was

associated with the tissue. At the intermediate dose, only ≈34% of the drug was recovered, and the variation in recovery was larger than observed at the high dose. These results suggest that a significant loss of the applied paclitaxel occurred before it reached the tissue.

In a separate set of in vitro experiments, drug retention on the stent after balloon mounting averaged only 52% of the applied dose (19.7 µg/stent), and additional losses (up to 17%) occurred during ex vivo manipulation subsequent to mounting. These losses may have resulted from cracking and flaking of the paclitaxel film caused by distortion of the stent during crimping. Simple handling of the stent before mounting resulted in <5% drug loss. Additional losses to the blood lipids may occur during the brief (≈30-second) exposure to the coronary circulation before deployment. This was demonstrated in washout experiments in which a 30-second exposure to pig blood at 37°C resulted in loss of <5% of the applied paclitaxel dose.

Discussion

In this study, a pig model of coronary stent restenosis was used to test whether local paclitaxel delivery would prevent neointimal hyperplasia induced by vascular stretch injury. Palmaz-Schatz stents were coated with a range of paclitaxel doses and were deployed with mild oversizing in the LAD. Preliminary experiments that applied paclitaxel by use of a nonbiodegradable (ethylene vinyl acetate) polymeric stent coating were marked by an intense inflammatory response, severe luminal narrowing, thrombosis, and death. To reduce these risks, we chose to eliminate the polymer and apply paclitaxel to the bare stent with a dip-coating technique (see Methods). We assumed that this approach would be optimal for rapid drug elution and high drug tissue concentrations because there is no barrier to prevent paclitaxel from gaining immediate access to the injured arterial tissue.

Locally applied paclitaxel produced a dose-dependent inhibition of neointimal formation, as revealed by the pattern of change in the angiographic and histomorphometric indices during the 4-week evaluation period. Analysis of the data by ANOVA showed that inhibition of the tissue hyperplastic response was significant (neointimal area, *P*<0.040; LLI, *P*<0.0028) or highly significant (luminal area, *P*<0.0004) over all treatment groups. In pairwise comparisons involving Dunnett's test, statistical significance was routinely observed when the high-dose treatment group was compared with the controls. Specifically, the LLI (Figure 2A) and luminal area (Figure 4B) showed the largest differences (84% for LLI; 90% for luminal area), whereas the percentage change in the MLD (46%) and neointimal area (39%) were less pro-

TABLE 3. Postimplantation Paclitaxel Recovery

Applied Dose, n µg	n	Stent, µg	Tissue, µg	Instrument,* µg	Total, µg	Recovery, %
16.7±1.6	6	3.36±1.75	2.28±1.39	0.02±0.005	5.65±2.17	33.8
		(59.4%)	(40.2%)	(0.3%)	(100%)	
177±8.5	4	63.68±8.45	55.43±13.92	0.93±0.860	120.02±15.03	67.8
		(53.0%)	(46.2%)	(0.8%)	(100%)	

*Paclitaxel removed from dissecting instruments

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