

# Local Drug Delivery via a Coronary Stent With Programmable Release Pharmacokinetics

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**Background**—Fixed drug release kinetics and vessel wall partitioning may limit the effectiveness of drug-eluting stents. We report preliminary experience using a new coronary stent with programmable pharmacokinetics.

**Methods and Results**—A newly designed metallic stent contains honeycombed strut elements with inlaid stacked layers of drug and polymer. In vitro studies evaluated recipes for loading paclitaxel to establish the parameters for controlling drug release. Manipulation of the layers of biodegradable polymer and drug allowed varying of the initial 24-hour burst release of paclitaxel from 69% to 8.6% ( $P < 0.0001$ ). Late release of drug could be adjusted dependently or independently of early burst release. A biphasic release profile was created by the addition of blank layers of polymer within the stack. In the 30-day porcine coronary model ( $n = 17$  pigs), there was a 70% reduction in late loss ( $0.3 \pm 0.5$  versus  $1.0 \pm 0.5$  mm,  $P = 0.04$ ), a 28% increase in luminal volume ( $132 \pm 12$  versus  $103 \pm 21$  mm<sup>3</sup>,  $P = 0.02$ ), and a 50% decrease in histological neointimal area ( $2.0 \pm 0.5$  versus  $4.0 \pm 1.6$  mm<sup>2</sup>;  $P < 0.001$ ) compared with bare metal controls. Temporal and regional variations in vascular healing were seen histologically.

**Conclusions**—Layered polymer/drug inlay stent technology permits flexible and controllable pharmacokinetic profiles. Programmable, complex chemotherapy using this approach may be feasible for the treatment of cardiovascular disease. (*Circulation*. 2003;107:777-784.)

**Key Words:** pharmacokinetics ■ stents ■ angioplasty ■ restenosis

Fixed drug release kinetics and vessel wall partitioning may limit the effectiveness of present drug-eluting stents.<sup>1-3</sup> A new type of metallic stent has been engineered specifically as a next-generation coronary drug delivery system that allows precise and programmable control over spatial and temporal release kinetics and substantially enhances drug-loading capacity. This study evaluated several recipes for loading paclitaxel as a model lipophilic agent to establish the parameters for controlling paclitaxel release. We also demonstrated that one such loading method is biologically effective when delivered in a porcine coronary model.

## Methods

### Stent Design

Figure 1 shows the balloon-expandable, 316L stainless steel backbone of the Conor MedSystems MedStent. The unique design features include honeycombed struts linked to flexible sinusoidal bridges by specially contoured features called ductile hinges. Unlike conventional stents consisting of repeating units where the entire structure is deformed by expansion forces placed on it, the MedStent differs in that deformation is confined to the 10% of the stent comprised of the ductile hinges rendering the struts as passive elements. This allows the struts to be cored with holes or cavities for drug delivery with no effect on the strength of the struts. Figure 1C

shows a finite element analysis of the applied stresses when holes are placed in a conventional stent without hinges. Before stent expansion, the holes are generally rectangular. On expansion, the holes deform, becoming rhomboidal, losing 15% to 20% of their cross-sectional area. In contrast, Figure 1D shows a Conor stent with ductile hinges, demonstrating that during stent expansion, the stresses and deformation are confined to the ductile hinges whereas all other stent elements remain unstressed, with no change in the shape or cross-sectional area of the holes. Similarly, because there are pairs of hinges on each side of the bridge sections, there is no net bending moment and therefore no rotation of the bridges during expansion. The holes can be inlaid with polymer/drug that will not deform or separate from stent during stent expansion, and bench testing shows no extrusion of polymer. Ten-year life-cycle fatigue testing showed no fractures or cracking of any stent component. The stents used were 3/15 mm with a strut thickness of 140  $\mu$  and had 588 laser-cut holes.

### Polymer/Drug Loading

Poly(lactide coglycolide) (PLGA) with the lactic acid to glycolic acid ratios of 50:50 and 85:15 (Birmingham Polymers) were dissolved in dimethyl sulfoxide (DMSO) to make concentrations of 5% for the PLGA 85:15 and 10% for the PLGA 50:50. Appropriate amounts of paclitaxel (Samyang Genex Co) were added to the polymer solutions to make final concentrations of 1% or 3%.

Polymer/drug solutions were shot into the holes from a piezoelectric nozzle with a 40- $\mu$ m orifice positioned by a micromanipulator.

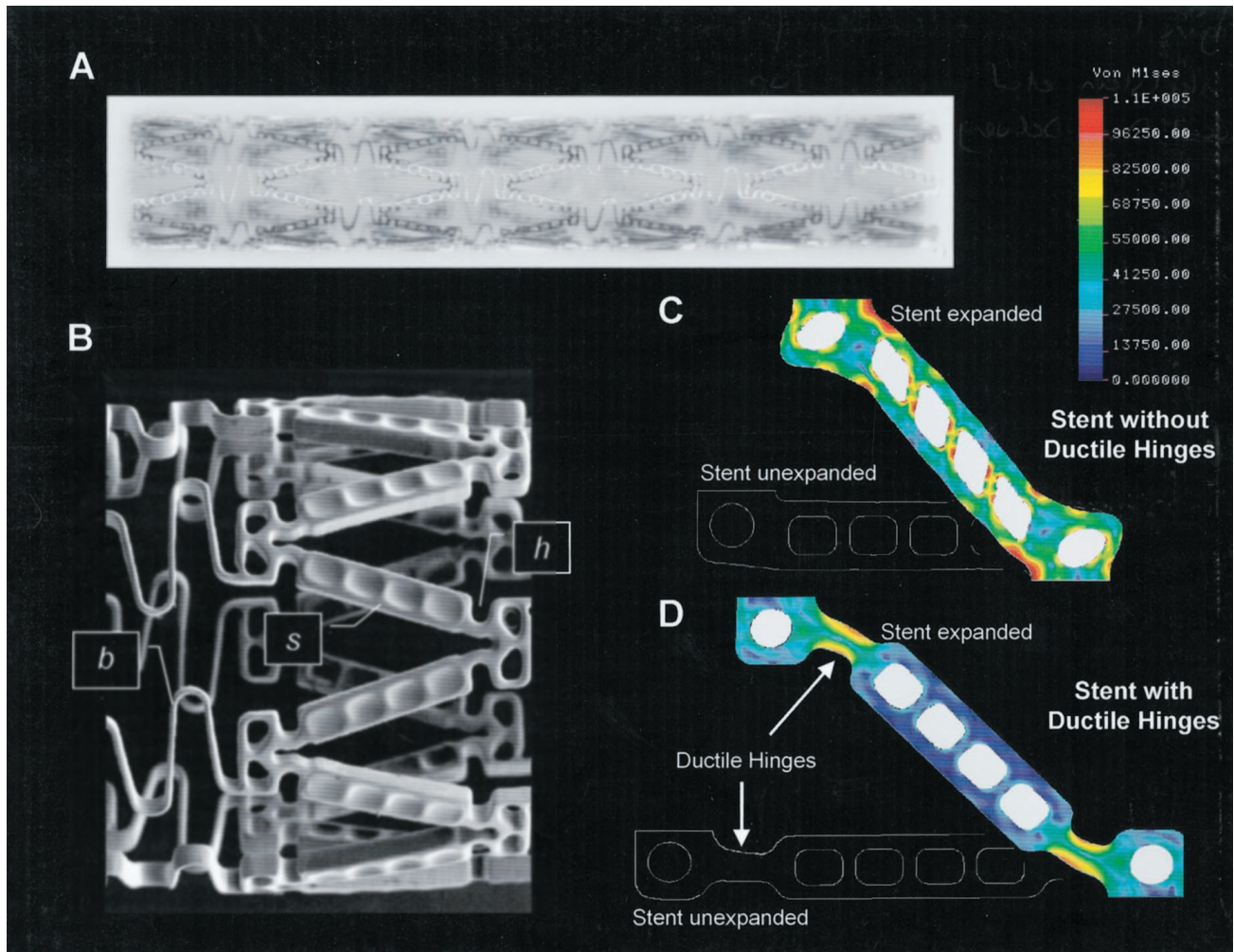
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**Figure 1.** A, 3/15 mm Conor stent metallic backbone. B, SEM of section of stent. s indicates struts with laser-cut holes, two thirds of which are filled PLGA polymer inlays; h, ductile hinges, and b, sinusoidal bridges. C and D, Finite element analysis of diameter expansion of stents with honeycombed struts without (C) and with (D) ductile hinges. Stent unexpanded (black and white) and stent expanded (color). Color-coded units are Von Mises shear stress.

The solvent evaporated in 30 minutes to leave a PLGA/paclitaxel layer inside the holes. The loading process was repeated on the same holes with as many as 22 layers.

For *in vitro* kinetic studies, individual layers were varied to create different stacking arrangements according to goals of the specific experiment. In addition to layers containing PLGA/paclitaxel, layer types without drug were added, including blank PLGA 85:15 to form a slower eroding film at the bottom of the holes and blank PLGA 50:50 to retard the release of paclitaxel. Processing variables, such as polymer molecular weight, viscosity, number of layers, layer thickness, drying time, temperature, humidity, and solvent type were found to influence kinetics and thus were tightly controlled.

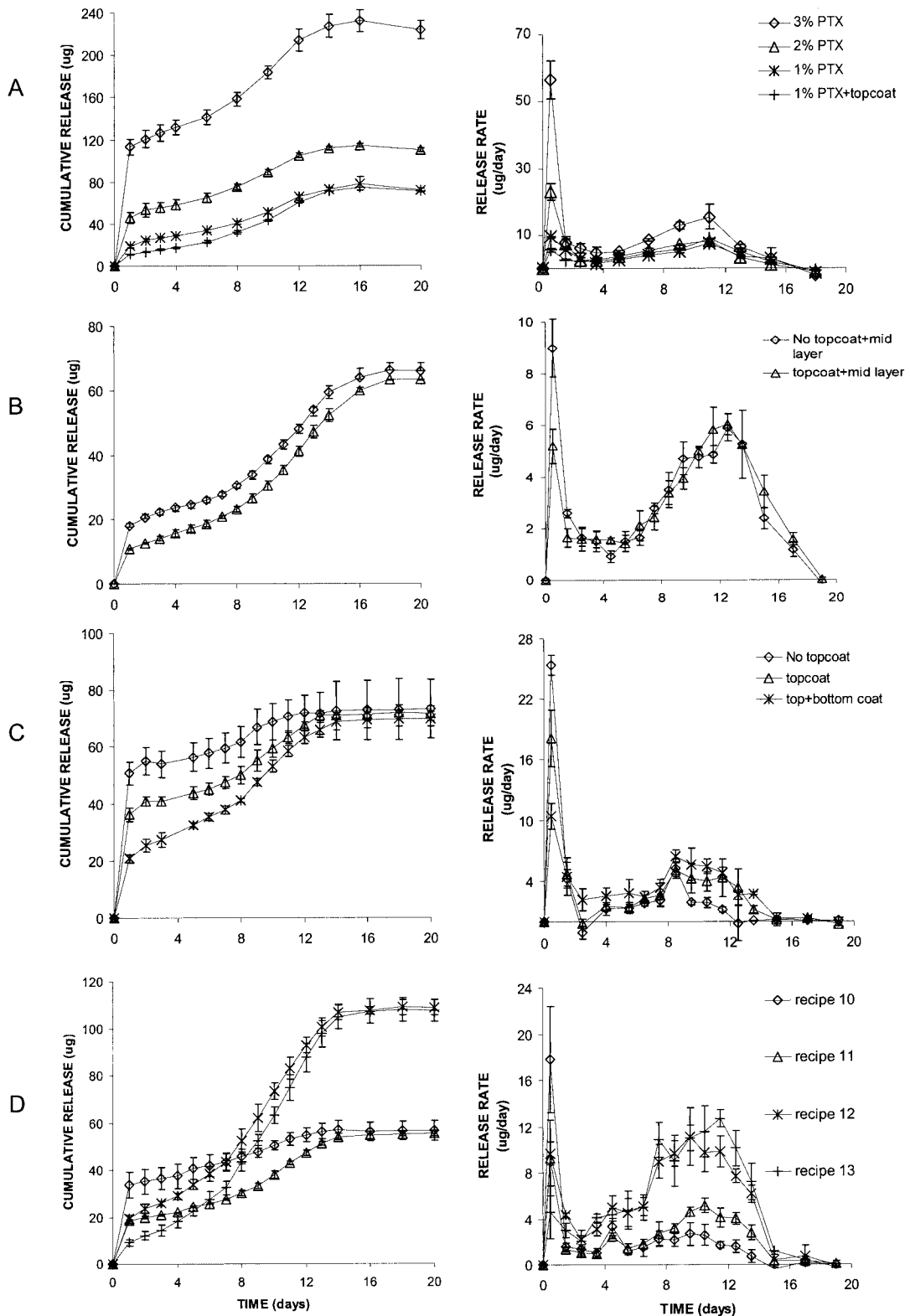
For animal experiments, the 392 holes on the struts bounded by the ductile hinges were filled with polymer/drug, and the remaining 196 holes near the bridges were left empty to evaluate the spatial effects of paclitaxel release. As a starting point for future comparisons, paclitaxel kinetics were chosen to simulate first-order release kinetics, as seen with coated stents. These stents were layered with stacks of 12 loadings of PLGA 50:50 (molecular weight 40 to 70 kDa) containing 1% paclitaxel to a total dose of 95  $\mu\text{g}$  of paclitaxel per stent. Approximately 60% of the drug was released by 24 hours and 100% released by 15 to 20 days. Stents were mounted on 3/20 mm PTCA balloons and sterilized with ethylene oxide.

### In Vitro Kinetics

Individual stents ( $n=52$ , 3 of each stacking type) were immersed in agitated 2-mL aliquots of 2 mol/L N,N-diethylnicotinamide (DENA) for serial 1- to 3-day periods, for a total duration of 20 days. The DENA was found to improve paclitaxel solubility from 0.45  $\mu\text{g}/\text{mL}$  in PBS to 980  $\mu\text{g}/\text{mL}$  (>2000-fold increase), approximating an infinite sink without requiring simulated flow conditions. The aliquots were injected into a Symmetry C18 column (Waters Corporation). The HPLC system was optimized to detect paclitaxel and to remove the interfering peaks from the DENA control. Stents were examined by scanning electron microscopy (SEM) at 0, 2, 6, 14, 22, and 24 days to verify extent of polymer erosion.

### Porcine Stent Restenosis Model

Animal experiments were approved by the Institutional Animal Care and Use Committee and conformed to AHA guidelines. Juvenile farm pigs (S & S Farms, Ranchita, Calif;  $n=17$ ) underwent placement of single coronary stents in the mid right coronary artery as previously described.<sup>4</sup> The pigs received 75 mg clopidogrel and 325 mg aspirin the day before and for 7 and 30 days thereafter, respectively. Stents with PLGA 95  $\mu\text{g}$  paclitaxel ( $n=6$ ) were compared with bare metal stents without holes ( $n=7$ ). To evaluate polymer toxicity, stents containing PLGA polymer without drug



**Figure 2.** Paclitaxel release kinetics experiments. Each curve represents 3 stents. A, Differing cumulative doses can be released, minimally affecting release kinetic profiles. B, Initial burst release rate can be independently controlled without affecting subsequent release kinetics and a two-step pulsatile release profile. C, Near first-order kinetics with a high but controllable burst release from stents with the same total dose. D, Demonstration of independent control over early-phase and late-phase drug release. PTX indicates paclitaxel.



(n=4) were similarly implanted. At 1 month, quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) were performed, followed by euthanasia under general anesthesia. The coronary arteries were perfusion-fixed and placed in formalin.

### Data Acquisition and Analysis

QCA parameters included proximal and distal reference, minimal lumen diameter (MLD), and late loss. Eleven IVUS frames (7 within the stent and 2 in the 6-mm segments both proximal and distal to the stent) were selected at 2.5- to 3-mm intervals for planimetry. Measurements included lumen and intimal volumes by Simpson's rule.

Tissue blocks were embedded in methyl methacrylate and ground into 3 cross-sections at predetermined points to avoid sampling bias. The 2 sections cut across drug-containing struts were analyzed separately from a middle section cut across the sinusoidal bridges. Stained Paragon sections were examined by an experienced pathologist (M.C.F.) using a prospectively defined grading scale.<sup>4</sup> Histomorphometric analysis of the tissue sections was performed with a Nikon E400 microscope and ImagePro software for measurement of the stent and lumen areas and mean neointimal thickness. Injury score was measured as described by Schwartz et al.<sup>5</sup>

### Statistical Analysis

All quantitative measurements and histological parameters were obtained by blinded observations. Data are summarized as mean±SD, unless otherwise specified. Comparisons for interval data were by unpaired Student's *t* test. Comparisons for ordinal data were by Mann-Whitney *U* test.

## Results

### In Vitro Release Pharmacokinetics

SEM showed that polymer erosion progressed as deepening concave-shaped exposed polymer surfaces, thereby increasing surface area over time. By 22 to 24 days, there was no residual polymer. Lumen-side PLGA 85:15 barrier layers took 14 to 22 days to erode through.

Figure 2 graphs cumulative paclitaxel release and daily release rates from 4 in vitro experiments. Figure 2A shows stents with 10 stacked layers containing different concentrations of paclitaxel. The top 3 curves show that drug release profiles are parallel and proportional to the total drug loaded. After 1 week, another slight increase in release rate was observed, possibly because of the enlarging surface area of PLGA. The bottom curve resulted from 3 additional topcoats of PLGA 50:50 devoid of drug but the same total amount of drug as in the 1% paclitaxel curve immediately above it. Top coating reduced the first 24-hour burst release from 24% to 14.7% of the total dose loaded ( $P<0.0005$ ). In Figure 2B, blank topcoats also reduced initial 24-hour burst release (26.9% to 16.8%,  $P<0.0002$ ). The exaggerated change in slope after day 10 resulted from placing blank layers of PLGA 50:50 in the middle of the stack, thus creating a biphasic drug release. Figure 2C shows that initial and late release rates can be varied in an inversely linked fashion by adding top and bottom blank layers. Figure 2D uses recipes analogous to Figures 2B and 2C to show that initial and late release rates can be varied independently. The 24-hour burst release was reduced to a minimum of 8.6% ( $P<0.0001$ ) by top coating (50:50) and bottom barrier layer (85:15). The late release of paclitaxel was affected by varying the concentration of drug, number of layers, and positioning of the various layers within the stack.

### Effects of Paclitaxel Release In Vivo

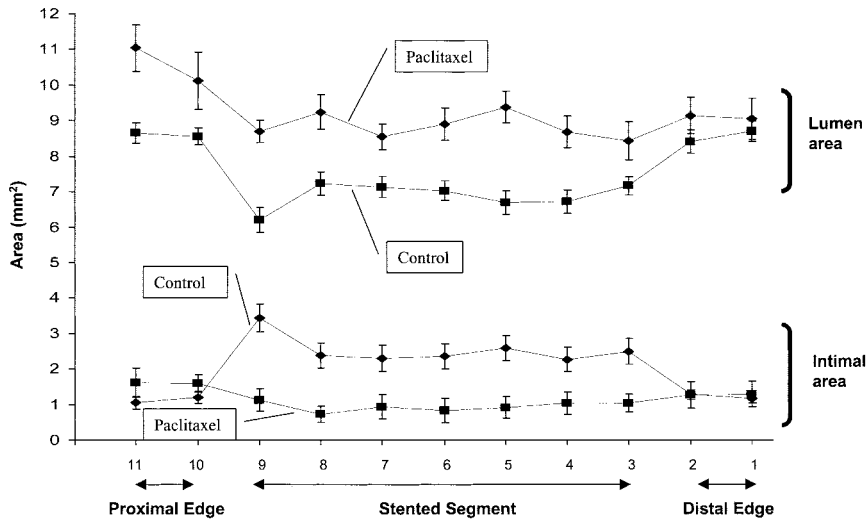
All animals survived for 1 month. Table 1 summarizes QCA, IVUS, and histomorphometric parameters. Baseline QCA indices did not differ between the drug delivery and the control metal stents. At follow-up, lumen dimensions were significantly improved in the paclitaxel group, with the MLD increasing by 50% ( $P<0.001$ ) and late loss decreasing by 70% ( $P=0.04$ ).

Follow-up IVUS pullback showed that the paclitaxel group had a 28% larger luminal volume ( $P=0.02$ ) and a trend toward 64% less neointimal volume ( $P=0.08$ ), with no evidence of worsening in the edge regions proximal and distal to the stent (Figure 3).

Histomorphometry revealed that injury score and stent area were similar in both groups whether at the strut or bridge regions of the stent. Lumen area, intimal area, percent area stenosis, and mean intimal thickness were significantly improved in the paclitaxel group in the strut/drug-containing sections. Similar but nonsignificant trends toward improvement were seen at the sinusoidal bridges of the paclitaxel-containing stents.

**TABLE 1. QCA, IVUS, and Histomorphometry**

	Bare Metal Controls	Paclitaxel	<i>P</i>
QCA, n	7	6	
Baseline			
Reference diameter, mm	2.8±0.2	2.9±0.1	0.8
Balloon/artery ratio	1.1±0.1	1.2±0.1	0.27
MLD, mm	2.8±0.2	3.0±0.2	0.07
Follow-up			
MLD at 1 month, mm	1.8±0.4	2.7±0.4	0.001
Mean lumen diameter, mm	2.2±0.3	2.9±0.3	0.001
Diameter stenosis, %	30±12	9±4	0.002
Late loss, mm	1.0±0.5	0.3±0.5	0.04
IVUS, n	7	6	
Follow-up			
Stent volume, mm <sup>3</sup>	141±19	147±10	0.5
Lumen volume, mm <sup>3</sup>	103±21	132±12	0.02
Intimal volume, mm <sup>3</sup>	38±30	14±5	0.08
Area stenosis, %	26±18	9.7±4.1	0.05
Histomorphometry			
Struts, n	14	12	
Injury score	1.8±0.2	1.7±0.3	0.4
Lumen area, mm <sup>2</sup>	3.9±1.1	5.6±1.5	0.002
Intimal area, mm <sup>2</sup>	4.0±1.6	2.0±0.5	0.0004
Area stenosis, %	49±13	27±10	0.01
Intimal thickness, mm, mean	0.45±0.20	0.16±0.1	0.0001
Bridges, n	7	6	
Injury score	2.0±0.2	1.8±0.4	0.9
Lumen area, mm <sup>2</sup>	3.7±1.0	4.5±1.7	0.3
Intimal area, mm <sup>2</sup>	2.9±1.4	1.9±0.8	0.15
Area stenosis, %	43±13	32±19	0.25
Intimal thickness, mean, mm	0.34±0.16	0.18±0.12	0.07



**Figure 3.** Graphs of lumen and intimal area during IVUS pullback. Data are shown as mean  $\pm$  SEM.

Figures 4 and 5 show histological sections, and Table 2 summarizes the scored histological features from strut and bridge locations. Bare metal controls were similar at the struts or the bridges, with a thickened neointima composed of morphological smooth muscle cells and extracellular matrix, mild scores for neointimal fibrin, and adventitial fibrosis. A neoendothelium consisting of a coherent layer of flat, elongated cells was seen, and there was minimal inflammation, foreign body reaction, or medial necrosis. The paclitaxel group had a very different and spatially specific histological appearance. Sections containing paclitaxel-loaded struts had voids where the polymer occupied the holes and consistently had grade 3 fibrin deposition surrounding the struts. There was partial healing with smooth muscle cells and extracellular matrix present between the struts. There was significantly more inflammation, foreign body reaction, medial necrosis, and adventitial fibrosis than in bare metal controls. Sections taken from the bridge locations showed that the paclitaxel group did not differ from bare metal controls, apart from a minimal increase in intimal inflammation. Both groups showed complete healing with intimal smooth muscle cells and matrix, a neoendothelial layer, and minimal medial necrosis. Sections containing stents with polymer and no drug were identical to bare metal controls, except for the persistent voids where the polymer had been in the strut holes.

### Discussion

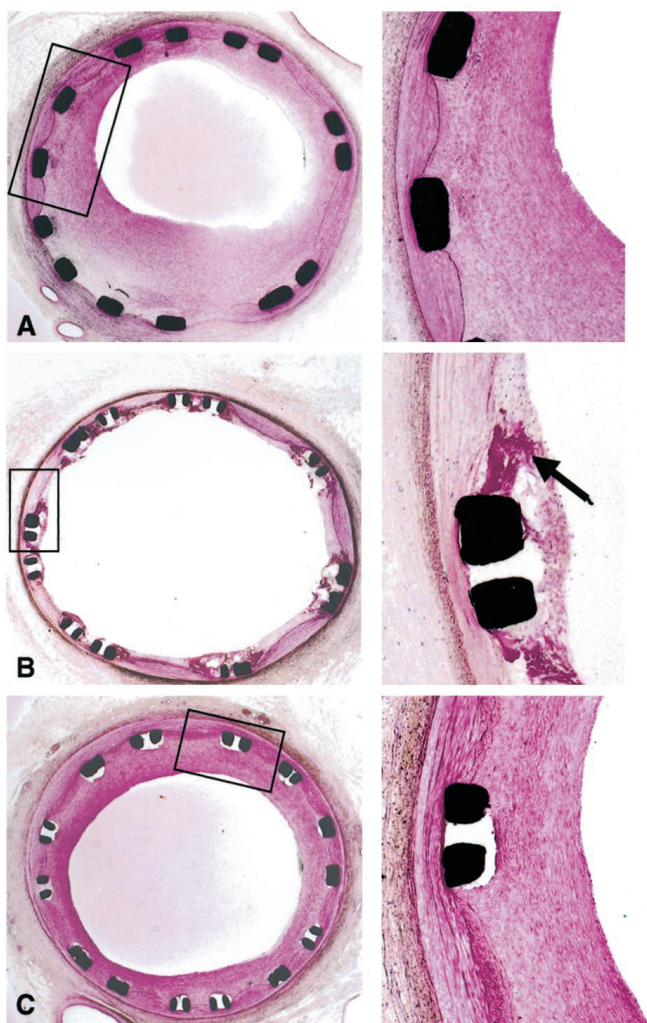
Early clinical studies using first-generation drug-eluting stents with sirolimus and paclitaxel have shown impressive reductions in 6- to 12-month restenosis and MACE rates in easier to treat coronary lesions.<sup>6,7</sup> Other stent trials delivering actinomycin-D or batimastat have been stopped because of apparent local drug toxicity. For the most part, these stent/drug platforms have used standard metallic stents coated with a thin (5 to 10  $\mu$ ) elastomeric biostable polymer surrounding the struts, yielding a low-volume, small-thickness, high-surface-area drug delivery system. Drug release rates approximate classic first-order kinetics, where a fixed fraction of elutable drug is released per unit time, as predicted by Fick's Law of diffusion.<sup>8</sup> Cumulative release curves show a large

percentage of drug is released in the first 24 hours and, in some cases, about one third of the drug remains on the stent indefinitely. These release kinetics are difficult to substantially alter, because they are governed by the physical chemical properties of drug and polymer and are proportional to surface area and inversely proportional to membrane thickness.<sup>2</sup> Early burst release can be somewhat retarded by adding a blank polymer topcoat at the expense of a thickening of the stent. The success and the toxicity of these stents may be related to the significant and rapid partitioning<sup>2,3</sup> of these lipophilic compounds in the adjacent vessel wall, thus creating a second drug depot. Possible late untoward effects include necrosis with aneurysm formation and stent malposition to the wall. Dehiscence or deformation of the surface polymer during expansion could affect release of drug from the polymer or, worse, embolize the polymer. Finally, available coated stents have yet to load enough drug to allow potentially less-toxic, nonpartitioning water-soluble drugs and biologic macromolecules such as peptides and oligonucleotides to be successfully delivered over a time course consistent with their mechanism of action.

Our study reports preliminary experience with a novel design drug-delivery stent loaded with paclitaxel as a model lipophilic agent. The Conor MedStent design differs from conventional drug delivery stents in that the stresses and strains of stent expansion are concentrated in small, specially contoured features called ductile hinges, which absorb all expansion forces. It is therefore possible to create holes or wells in the struts without sacrificing strength, scaffolding, or flexibility. The holes are filled with therapeutic drugs in a layered configuration, creating hundreds of individually adjustable drug reservoirs. Compared with conventional stents with a 5- to 10- $\mu$ m coating, the MedStent's polymer/drug volume is enlarged by 4- to 16-fold, polymer thickness is increased 14- to 28-fold, and polymer surface area is reduced by 64% to 81%. These features permit expanded drug-loading capacity, the ability to deliver multiple drugs in a specified sequence, and the ability to program the timing and spatial distribution patterns of drug release.

In vitro studies demonstrated that drug-release kinetics are flexible and programmable. Reproducibility of the kinetic

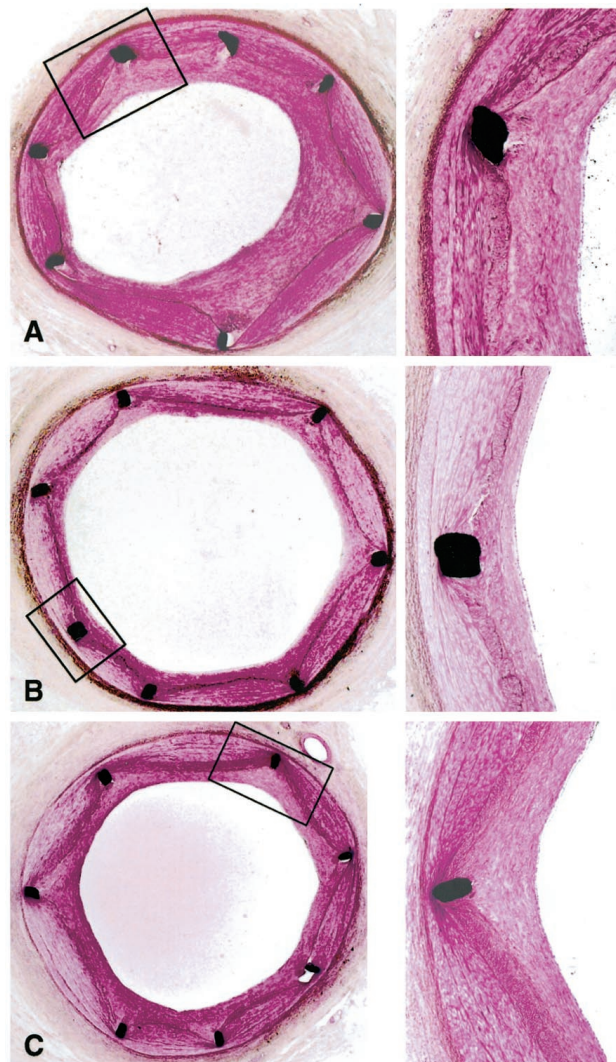




**Figure 4.** Representative sections of arteries at site of stent struts (paragon stain at  $\times 20$  and  $\times 80$  magnification; strut thickness,  $140\ \mu$ ). A, Bare metal control. Healing is complete with fibromuscular neointima covering struts (S). B, Paclitaxel stent. At site of struts where the drug is present, healing is not complete, with residual fibrinoid deposits present (arrow). C, Control with polymer but no drug. Healing is complete, as with the bare metal control shown in panel A.

profiles was suggested in several instances by the small variability between samples but not quantifiable because of the small number of samples per group. Drug release was controlled so that a wide range of dosages was deliverable without affecting the general shape of the kinetic release profile and thus facilitating dose-response studies. Initial 24-hour burst release was selectively variable from  $>60\%$  to  $<10\%$  of the total dose. Burst rates were controllable, with minimal alteration of chronic release rates. A two-step early and late pulsatile release was demonstrated, as was independent control over the magnitude of the early and late phases.

Studies in the 30-day porcine coronary stent model showed that paclitaxel delivered with a first-order kinetic profile from two thirds of the holes was biologically active, inhibiting neointimal thickening and delaying healing in close proximity to the drug-containing cavities. When stents with PLGA



**Figure 5.** Representative sections of arteries at site of stent bridges (Paragon stain at  $\times 20$  and  $\times 80$  magnification). A, Bridge from bare metal control. Healing is complete with bridge (B) covered by the fibromuscular neointima. B, Bridge from paclitaxel stent. C, Control with polymer but no drug in any part of the stent.

50:50 but without drug were implanted, there was no demonstrable toxicity.

These preliminary studies have several limitations that should be considered with respect to making inferences about future clinical applications. Only a single drug was used to evaluate control over pharmacokinetics. Other agents were not tested, because the emphasis of this study was on stent mechanics and release pharmacokinetics. Paclitaxel was chosen as the model small molecule lipophilic agent because of a well-known mechanism of action and previously documented arterial wall responses.<sup>9-11</sup> Only one dose of paclitaxel and one kinetic profile were used in the pilot animal study, because this was designed to be illustrative of biological effect using the new device rather than being exhaustive with respect to quantitation or to compare with conventional surface-coated drug-eluting stents. Although the numbers of animals used were small, the results were consistent and

TABLE 2. Histology

	Bare Metal Controls	Paclitaxel	<i>P</i>
Struts, n	14	12	
Neointima			
Extracellular matrix	1.93±0.62	1.75±1.22	0.8
Inflammation	0.21±0.43	1.92±0.79	0.0001
Foreign body reaction	0.07±0.27	1.17±1.03	0.001
Fibrinoid deposits	1.07±0.27	2.92±0.29	0.00001
Media			
Fraction missing	0.09±0.13	0.18±0.24	0.3
Necrosis	0.43±0.51	2.50±0.67	0.00002
Fibrosis	0.07±0.27	0.08±0.29	0.9
Inflammation	0.00±0.00	0.00±0.00	-
Adventitia			
Fibrosis	1.21±0.58	2.25±0.87	0.004
Inflammation	0.64±0.74	1.08±0.29	0.05
Bridges, n	7	6	
Neointima			
Extracellular matrix	1.71±0.7	1.67±0.82	0.9
Inflammation	0.00±0.00	0.50±0.55	0.04
Foreign body reaction	0.14±0.35	0.00±0.00	0.4
Fibrinoid deposits	0.86±0.35	1.17±0.41	0.2
Media			
Fraction missing	0.20±0.20	0.17±0.23	0.7
Necrosis	0.43±0.5	0.50±0.84	0.9
Fibrosis	0.29±0.45	0.17±0.41	0.6
Inflammation	0.00±0.00	0.00±0.00	1.0
Adventitia			
Fibrosis	1.71±0.88	2.17±0.75	0.4
Inflammation	0.86±1.12	1.00±0.63	0.5

Graded on a 0 to 3 scale from Makkar et al (reference 4). 0 indicates minimal; 1, mild; 2, moderate; and 3, severe.

corroborated by independent measurement methods, thus permitting valid statistical inferences. The finding of incomplete healing (persistent fibrin and inflammation) suggests that the present dose may have been too large or delivered too rapidly or the duration of follow-up too short.<sup>12,13</sup>

These limitations notwithstanding, our observations were consistent with previous porcine coronary studies delivering paclitaxel from surface-coated stents showing incomplete vascular healing at 1 month.<sup>9–11</sup> By programming the Conor stent not to have polymer/drug in proximity to the sinusoidal bridges, we were able to demonstrate localized control over the spatial distribution of drug effects. We found islands of healed vessel wall with less reduction in neointimal thickening localized to the bridge sections and interstrut regions. These findings infer regional dose effects and raise the question that localized healed regions may be a scaffold to promote late complete vessel wall healing. This localized dose effect is consistent with the known partitioning behavior of paclitaxel, which is associated with large spatial concentration variations, resulting in concentrations that may be either toxic or inadequate.<sup>2,3</sup>

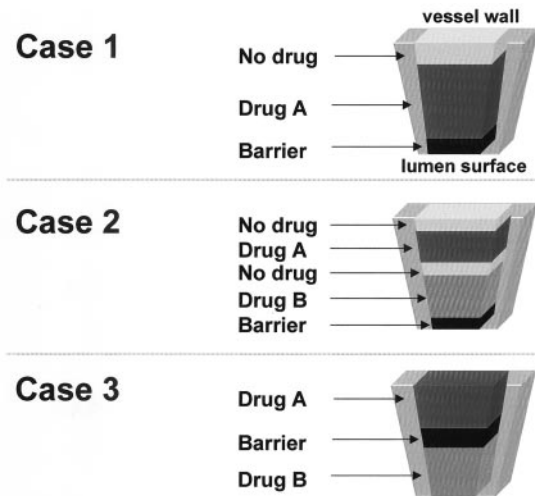


Figure 6. Schematic of 3 polymer/drug layering combinations in a strut hole.

Additional work with the MedStent has included loading oligonucleotides. The system of filling individual holes one layer at a time is now fully computer automated, enhancing speed and scalability. Within any given hole, the stacking of inlaid polymer/drug can be varied to create a variety of controllable pharmacokinetic profiles. Figure 6 illustrates some of the potential programmability features of the MedStent. In case 1, and as demonstrated *in vitro*, a more slowly degrading barrier layer has been placed at the lumen-side surface of the hole, thus preferentially causing more rapid egress of drug in the direction of the wall. A topcoat containing no drug reduces burst release. Case 2 is an example showing how multiagent chemotherapy might be delivered to the peristrut vascular wall with early release of drug A and delayed release of drug B. Case 3 shows a method to deliver multitarget chemotherapy, with drug A localized to the stented wall and drug B eluted into the lumen for simultaneous treatment of vulnerable plaque or diffuse disease.

That preferential vectorial delivery in the direction of the wall or lumen may be achievable is suggested by three observations. First, the major mechanism of drug release is polymer erosion rather than diffusion. This is almost certainly the case, because release profiles are controllable on the basis of concentration of drug in sequential layers. More water-soluble agents may have different release kinetics governed by diffusion as well as bulk erosion. Next, the specific use of slower degrading polymer on luminal side with stacked layers of faster degrading PLGA on top reduced initial burst rates and delayed release rates in kinetic curves to the extent expected if all drug could only elute toward the side. Finally, serial SEMs *in vitro* confirm that the slower-degrading PLGA barrier on the lumen side does not erode through until 16 to 20 days. Although there is no present data showing an advantage of multiagent chemotherapy for preventing restenosis, such treatment may be considered in light of early reports, with single-agent paclitaxel and sirolimus having restenosis particularly at the edges.

Finally, our studies suggest that present methods of local drug delivery from vascular stents can be viewed in a perspective analogous to the progress in developing systemically administered drugs. In the past, systemic medication therapy was limited by the fixed pharmacokinetics of specific drugs. Combining drugs with controlled-release methodology to create flexible hybrid delivery platforms, thereby decoupling chemical and kinetic properties, has revolutionized systemic therapy. Preliminary experience with a second-generation programmable controlled-release stent technology suggests that similar approaches may be feasible for the interventional treatment of cardiovascular disease.

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