# Nonstent Drug Delivery

Current data on the use of drug-eluting balloon angioplasty to treat atherosclerotic arterial disease are limited but hold promise.

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The mechanisms of coronary restenosis after balloon angioplasty include (1) acute vessel recoil, (2) negative remodeling, and (3) neointimal hyperplasia. Stainless steel stents have become the default therapy in percutaneous coronary artery revascularization and have largely eliminated the influence of recoil and negative remodeling on restenosis; additionally, drug-eluting stents have attenuated the component attributable to neointimal hyperplasia. Despite this, restenosis still occurs, as does stent thrombosis, and the concern of late stent thrombosis, primarily in drug-eluting stents, continues to linger. In this context, the concept of local delivery of antiproliferative agents without stent placement invites renewed attention.

## BACKGROUND AND RATIONALE

Investigations aimed at catheter-based methods of local drug delivery date back to the pre-stent era, with the principal limitations being drug choice and delivery of the optimal dose, neither of which was sufficiently defined prior to the widespread acceptance and availability of stents.

The relative advantages of a drug-eluting balloon angioplasty strategy may be considered as follows:

- There is no foreign body left behind in the vasculature, thus perhaps reducing the absolute requirement for potent, prolonged, dual-antiplatelet therapy to prevent stent thrombosis.
- In contrast to drug-eluting stents, in which the active drug is delivered only to the arterial wall in contact with the stent struts (a minority of the total surface area of the treatment site), a greater vessel surface area could be exposed to the active drug.
- In anatomic situations where stenting may potentially be problematic (ie, bifurcations with important side branches).
- Stenting is not desirable due to vessel mechanics (significant arterial tortuosity leading to hinge points created by stents and/or locations, such as the common femoral artery, popliteal artery, and axillary artery in which flexion and rotational forces may lead to metal fatigue and stent fracture) or exposure to external compressive forces (common femoral artery, superficial femoral artery, infrapopliteal artery, and axillary artery).
- A stent is not deliverable due to significant proximal tortuosity and/or calcification.
- The potential of cost savings may exist.

These potential advantages need to be balanced by the possibility that a suboptimal balloon angioplasty result and threatened vessel closure may necessitate stenting anyway. Additionally, in patients in whom acute recoil or later negative remodeling may be an important mechanism of restenosis (diabetic patients, for example), balloon angioplasty alone may be insufficient.

## WHICH DRUG, WHY, AND HOW?

Our understanding of the spectrum of drugs that may be effective in this strategy is incomplete. The available literature has reported on the efficacy of paclitaxel in reducing neointimal inhibition, late lumen loss, and restenosis. The antirestenotic effect of paclitaxel on a drug-eluting stent platform has been well validated in randomized clinical trials[1] and in several years of subsequent worldwide clinical use. The reason for the efficacy of paclitaxel when utilized as part of a balloon delivery

| TABLE 1. RESULTS OF QUANTITATIVE CORONARY ANGIOGRAPHY IN A PORCINE CORONARY MODEL COMPARING PACLITAXEL-COATED BALLOON ANGIOPLASTY TO CONTROLS, ANIMALS TREATED WITH PACLITAXEL IN THE CONTRAST MEDIUM, AND ANIMALS TREATED WITH SIROLIMUS-ELUTING STENTS[a] | | | | | |
|---|---|---|---|---|---|
| **Parameter** | **Control (n = 11)** | **Paclitaxel in Contrast Medium (n = 12)** | **DEB (n = 11)** | **SES (n = 10)** | ***P* Value** |
| **At time of intervention** | | | | | |
| Reference diameter (mm) | 2.34 ± 0.13 | 2.47 ± 0.14 | 2.34 ± 0.13 | 2.67 ± 0.13 | .168 |
| Stent diameter (mm) | 2.92 ± 0.13 | 2.88 ± 0.15 | 2.89 ± 0.13 | 3.15 ± 0.13 | .313 |
| Overstretch ratio | 1.24 ± 0.06 | 1.18 ± 0.05 | 1.25 ± 0.06 | 1.22 ± 0.06 | .819 |
| **At 4-week follow-up** | | | | | |
| Reference diameter (mm) | 2.13 ± 0.15 | 2.39 ± 0.18 | 2.35 ± 0.15 | 2.37 ± 0.16 | .504 |
| Minimal lumen diameter (mm) | 2.02 ± 0.13 | 2.25 ± 0.14 | 2.76 ± 0.13 | 2.41 ± 0.14 | .004 |
| Late lumen loss (mm) | 1.00 ± 0.18 | 0.64 ± 0.20 | 0.14 ± 0.18 | 0.79 ± 0.18 | .006 |

*Abbreviations: DEB, drug-eluting balloon angioplasty; n, numbers of vessels; SES, sirolimus-eluting stent.*
*[a]Data are mean ± standard deviation.*
*(Adapted from Speck U, et al. Radiology. 2006;240:411-418).[2]*

system has been postulated to be due to its extremely hydrophobic/lipophilic nature, allowing it to pass through the hydrophobic barrier of cell membranes,[3] as well as its prolonged antiproliferative action despite brief drug exposure.[4] In contrast, the relatively hydrophilic compound, reviparin, is delivered much less effectively.[3] Although stents that elute rapamycin have also been demonstrated to be effective in reducing restenosis in randomized trials,[5] it is unknown whether it would be similarly deliverable and effective in a drug-eluting balloon platform. In a porcine coronary overstretch injury model, zotarolimus-coated balloon angioplasty has recently been shown to reduce neointima proliferation (Bodo Cremers, MD, and Ulrich Speck, MD, written communication, May 2009).

Several methods to effect local drug delivery have been tested, but three strategies have reported a relatively consistent drug effect on the vessel wall utilizing paclitaxel as the active drug: (1) a porous balloon with holes through which a fixed volume of the drug is injected at a low pressure (high pressure may result in vessel barotrauma),[6] (2) a conventionally designed angioplasty balloon coated with paclitaxel at varying doses, although most often reported at 3 μg/mm$^2$,[7,8] and (3) a double-balloon system entailing a proximal and distal balloon, proximal infusion port, and dwell space between the two balloons (Figure 1).[2,9] The addition of paclitaxel to radiocontrast material has also been reported to prevent restenosis in a porcine model.[10]

Studies suggest that after angioplasty with a paclitaxel-eluting balloon coated at 3 μg/mm$^2$, approximately 4% of the drug remains on the balloon, whereas 90% is released into the blood stream.[8] In a porcine model, approximately 2% of the total paclitaxel dose could be detected in the vessel wall.[3] In a rabbit study, paclitaxel could be measured transiently in circulating blood (up to 30 minutes) at a mean concentration of 35.5 ng/mL at 5 minutes,[6] which is 1/100 or less of the peak concentration that may occur in patients being treated with paclitaxel for solid organ tumors.

In comparison, the commercially available paclitaxel-eluting stent is coated at a concentration of 100 μg /cm$^2$, or 1 μg/mm$^2$, which occurs on the stent strut surface and releases in a bimodal pattern that is largely completed over 4 weeks.

## ANIMAL DATA

A number of animal studies have demonstrated an apparent reduction in neointima formation after balloon angioplasty. In a rabbit model of carotid stenosis (created using transmural electrical stimulation), paclitaxel delivery through a porous angioplasty balloon resulted in a reduction in neointimal area (0.13 ± 0.11 mm$^2$ vs 0.29 ± 0.18 mm$^2$ for untreated animals; $P < .05$) and a lower degree of stenosis (14 ± 11% vs 41 ± 18% for untreated animals; $P < .05$).[6] Also, by using a similar rabbit carotid injury model, local delivery of paclitaxel via a double-balloon delivery system reduced neointima formation. This positive effect was also noted even when bare-metal stent implantation was carried out at the target site, although

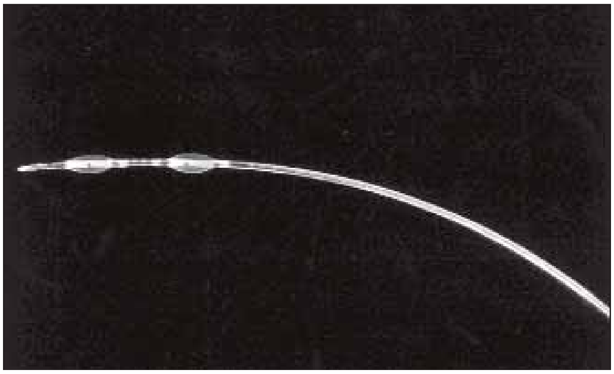

Figure 1. A double-balloon perfusion catheter. Two compliant balloons, proximal and distal, are employed. A proximal port exists through which the drug can be infused into the dwell space between the two balloons. (Reprinted with permission from Oberhoff M, et al. Cathet Cardiovasc Intervent. 2001;53:562-568).[9]

the absolute magnitude of neointimal formation was greater after stenting compared with angioplasty alone (Figure 2).[11] This reinforces the notion that stenting in and of itself induces a greater level of vessel injury than angioplasty alone. In contrast, in a porcine coronary model of deep metallic coil induced injury,[12] paclitaxel delivery via a double-balloon catheter prior to bare-metal stent implantation did not attenuate neointima formation measured at 28 days.[9] In a porcine carotid artery (no injury) model, paclitaxel-coated balloon (5 µg/mm$^2$) angioplasty prior to stent deployment markedly attenuated neointimal formation even with very brief (10–60 second) inflation times.[13] In a porcine coronary model with oversized stent deployment (1.2:1 stent-to-artery ratio), a paclitaxel-coated balloon angioplasty resulted in a larger minimum lumen diameter and less late loss than in control animals, in animals treated with paclitaxel in the contrast medium, and in animals treated with rapamycin-eluting stents (Table 1).[1] The variable response on neointimal inhibition in conjunction with stent implantation may relate to differences in methodology, including the arterial bed studied, animal species utilized, presence or absence of induced injury in the model, and perhaps, the method of drug delivery.

## CLINICAL DATA

The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease Small Vessel Disease (PEPCAD 1 SVD) trial was a single-arm study (120 patients) of small-vessel disease (2.25–2.8 mm) that showed that successful paclitaxel-eluting balloon angioplasty resulted in a 5.5% restenosis rate; when adjunctive bare-metal stent implantation was required for suboptimal angioplasty results (28% of patients), a 19% restenosis rate was observed if the stent was placed entirely within the portion of the artery exposed to paclitaxel, but was substantially higher if the stent included a vessel that had been untreated with drug ("geographic mismatch" was a concept that was raised in the days of intracoronary brachytherapy). In the PEPCAD II ISR trial, 131 patients with in-stent restenosis (ISR) were randomized between paclitaxel-eluting balloon angioplasty versus stenting with the Taxus device (Boston Scientific Corporation, Natick, MA). The primary outcome measure was 6-month late lumen loss. Secondary outcome measures included procedural success, 6-month

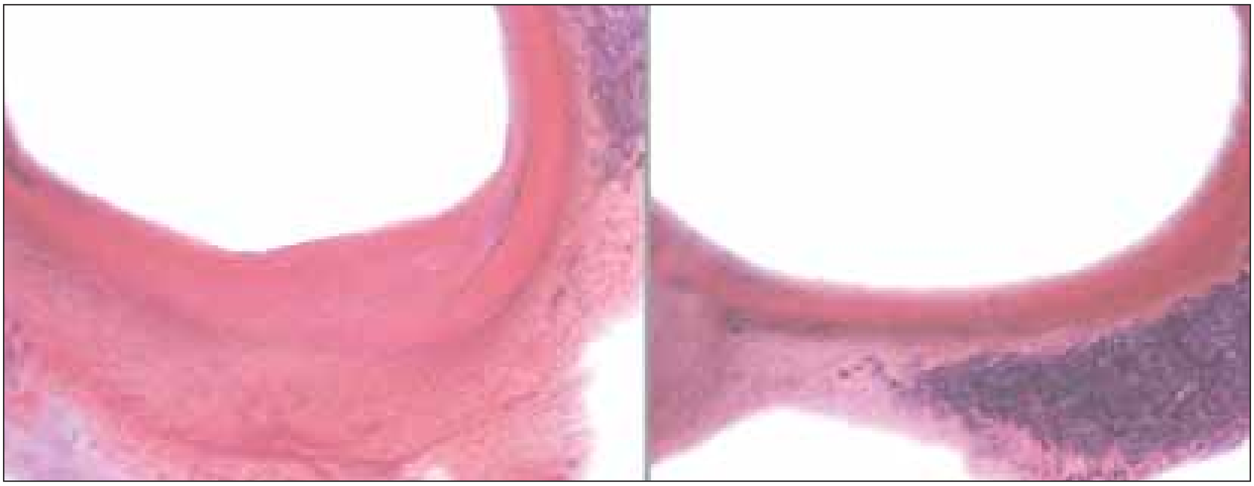

Figure 2. The effect of local delivery of paclitaxel on neointima formation 6 weeks after stent implantation or balloon dilatation in porcine coronary arteries. Note that although paclitaxel delivery reduces the neointima formation after either balloon dilatation or stent implantation, the magnitude of neointima generated is higher after stenting compared to balloon dilatation only (*P* < .01 compared to controls). (Reprinted with permission from Herdeg C, et al. Thromb Res. 2008;123:236-243).[11]

binary restenosis rate, and major adverse cardiac events (MACE) at 6 months, 1 year, and ultimately, 3 years. Late lumen loss was more favorable with drug-eluting angioplasty compared to restenting (0.20 ± 0.45 mm vs 0.45 ± 0.68 mm; *P* = .02); binary restenosis trended to be better as well (7% vs 20.3%; *P* = .06). Using an intention-to-treat analysis, MACE was lower in the drug-eluting balloon group (7.8% vs 16.9%; *P* = .20); however, this result did not achieve statistical significance. Analysis of the results, with regard to the treatment received, demonstrated a significant benefit of using drug-eluting balloons in terms of MACE (4.7% vs 18.3%; *P* = .02), largely driven by a significant decrease in target lesion revascularization (TLR) rates (3.1% vs 16.7%; *P* = .02).[14] An additional published ISR study, the Treatment of In-Stent Restenosis by Paclitaxel-Coated Balloon Catheters (PACCOCATH ISR) randomized 52 patients with ISR to either paclitaxel-coated balloon angioplasty or uncoated balloon angioplasty and demonstrated a marked benefit with paclitaxel-eluting angioplasty (Figure 3).[8] The primary endpoint of late lumen loss was markedly reduced (0.03 ± 0.48 mm vs 0.74 ± 0.86 mm; *P* = .002), as were restenosis (5% vs 43%; *P* = .002), MACE (4% vs 31%; *P* = .01), and TLR (0% vs 23%; *P* = .02). The DEBUIT study demonstrated that a strategy of drug-eluting balloon angioplasty of the main branch and side branch of bifurcation lesions with bare-metal stenting of the main branch may hold promise, although the study was small, and only a 4-month clinical outcome without angiographic follow-up was reported.[7]

Two published trials, the Thunder trial[15] and the more recently published FemPac trial,[16] demonstrated similar advantages of paclitaxel-eluting balloon angioplasty in atherosclerotic lower extremity arterial disease. The FemPac trial included 87 patients with femoropopliteal disease who were randomized to paclitaxel-coated balloon angioplasty versus conventional angioplasty for lesions of approximately 6 cm in length. The trial demonstrated significant reduction in late lumen loss and angiographic restenosis 6 months, although follow-up angiography rates were only 69% and 81% in the treatment and control arms, respectively. Six-month TLR rates were also improved (9% vs 33%) and although the difference between treatment arms persisted at 18–24 months, TLR events continued to accumulate between 6 and 24 months of follow-up, serving as a reminder of the prolonged restenosis window that may be observed in noncoronary endovascular interventions.

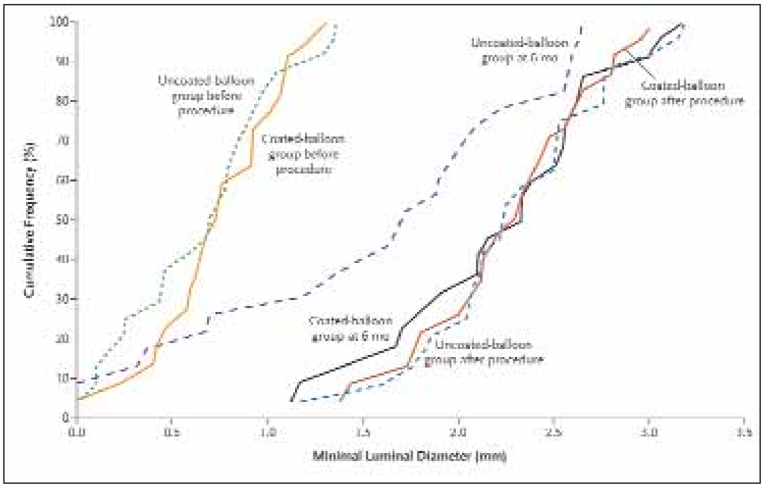


**Figure 3. Cumulative frequency distribution curve of in-segment minimum luminal diameter on quantitative coronary angiography in ISR lesions treated with paclitaxel-coated balloon angioplasty versus uncoated balloon angioplasty. (Reprinted with permission from Scheller B, et al. N Engl J Med. 2006;355:2113-2124).[8]**

## CONCLUSION

The data that are currently available regarding the applicability of drug-eluting balloon angioplasty as a stand-alone clinical treatment strategy for atherosclerotic arterial disease are limited but hold promise. The data in both animal models and small human trials are concordant; neointimal hyperplasia is reduced, as are late lumen loss, restenosis, and repeat revascularization. Obviously, much larger clinical studies would be needed to support widespread adoption into clinical practice.

However, some lingering issues need to be addressed. We must be cognizant of the fact that stents have allowed us, in almost all percutaneous coronary intervention (PCI) cases, to reliably achieve a good acute angiographic result and have substantially reduced the need for emergency coronary artery bypass grafting and repeat PCI within the first 24 hours, largely by reducing abrupt and threatened vessel closure that occurred after percutaneous transluminal coronary angioplasty. Even if a strategy of drug-eluting balloon angioplasty is convincingly demonstrated to reduce restenosis and TLR rates in large randomized trials, it cannot be expected to attenuate the risk of abrupt vessel closure early after angioplasty. Additionally, in lesions or patients with acute recoil or negative remodeling that may importantly influence restenosis risk after percutaneous transluminal coronary angioplasty, the presence of a stent may be critically important in reducing TLR rates.

Therefore, if adjunctive stenting is employed after drug-eluting balloon angioplasty, which may be required in cases of suboptimal angiographic result after angioplasty, clinical trials are required to demonstrate that the benefit will persist. Some animal data have suggested the contrary in this regard,[9] and this will warrant further investigation. The concept of "geographic miss" from the intracoronary brachytherapy era—dilating or stenting outside the zone of radiation treatment, thus increasing the likelihood of repeat restenosis—may also be important in drug-eluting balloon angioplasty, as suggested by the PEPCAD I data. The limited data for ISR are promising, but whether this strategy will prove effective for drug-eluting stent ISR is unknown.

In the coronary circulation, drug-eluting balloon angioplasty, if proven efficacious, likely holds the greatest promise for lesions in which stent deployment is technically challenging or unattractive (distal lesions in which stent delivery proves to be difficult, very angulated segments, small vessels, bifurcation disease). However, this treatment could prove useful in other lesions in which an excellent angiographic result can be achieved with angioplasty alone, obviating the need for stenting. Whether that will lead to a reduction in the cost associated with PCI is uncertain, but it is possible if stent utilization declines and the production costs of drug-eluting balloons are not prohibitive. Whether a drug-coated balloon is the best method of drug delivery (versus other strategies that have been described above) may also be debated; to be broadly applicable, any delivery strategy that is employed needs to be relatively easy to manufacture at a reasonable cost if it is to compete effectively with drug-eluting stents. Drug-eluting balloon angioplasty could also significantly impact the endovascular management of noncoronary atherosclerotic lesions in which restenosis remains an important limitation; also, the financial and clinical trial investment to test drug-eluting stent platforms has been insufficient. Femoropopliteal disease, in which stenting is less attractive anyway due to mechanical forces, is an obvious potential application,[15,16] as would be complex renal arterial disease (bifurcations, small accessory arteries).[17,18] These are vascular beds in which there is a dearth of good, randomized, sufficiently powered clinical trials and a relatively high rate of TLR that may allow for samples sizes that need not be as large as those required in coronary trials; therefore, these may be the areas on which to focus in designing drug-eluting balloon trials that are not cost-prohibitive.

Toxicities and side effects of paclitaxel at these doses for a brief duration of exposure should not be a significant concern, but will also have to be addressed in efficacy trials. Whether other antiproliferative agents can be delivered effectively in this manner is unclear, but may be moot if paclitaxel is proven to be reliably and consistently effective.

The concept of drug-eluting balloon technology is a potentially attractive option for some portion of coronary and noncoronary endovascular revascularization procedures, but further investigation needs to be completed to prove its benefit in a defined population. ■

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