Local drug delivery for the treatment of vascular disease has been studied for many years. In coronary artery disease, drug eluting stents are routinely deployed. However, with concerns regarding late thrombosis, and clinical applications where stenting is not desirable, such as peripheral vascular disease, a new direction to “leave nothing behind” has emerged. In Europe, paclitaxel-coated balloons have shown promise in reducing restenosis in both peripheral and coronary applications. However, a number of technical, economic and regulatory limitations of the current devices have been identified. Local or targeted fluid delivery of drugs may offer a relatively simple solution.

KEY WORDS: Endovascular procedures - Angioplasty, balloon - Paclitaxel - Stents - Drug delivery systems.

Drug-coated balloons

In Europe, balloons coated with paclitaxel have “burst” onto the interventional scene, inspiring a
new mantra for intervention — “Leave Nothing Behind”. For certain coronary applications (small vessels, bifurcations and in-stent restenosis of bare metal stents), the German Consensus Group has already recommended use of these devices to prevent restenosis (Class IIa, Level B). At least eight companies have commercial products available for coronary or peripheral vascular indications. All have a paclitaxel dosage of either 2 or 3 micrograms per square millimeter of balloon surface area, but differ only in the use of or type of coating matrix (excipient) combined with the drug. The first report of a randomized study of a drug-coated balloon was published in 2006. In this study, 52 patients with coronary in-stent restenosis were randomized to a standard (uncoated) balloon catheter or to an iopromide-paclitaxel-coated balloon catheter (“Paccocath”). At 6 months, the Paccocath group had significantly less neointimal tissue growth. In an extension of this study, an additional 56 patients with coronary in-stent restenosis were randomized, and the entire cohort was followed up to 2 years. At 24 months, the positive outcome was maintained, and the Paccocath group had significantly less target lesion revascularization (6% vs. 37%). Two randomized clinical studies in femoro-popliteal disease showed similar positive outcomes for the Paccocath balloon, which also were maintained out to 24 months. Many of the other DCBs commercially available in Europe demonstrated positive results in randomized clinical trials, and meta-analyses of randomized trials in femoropopliteal disease and coronary in-stent restenosis concluded that paclitaxel-coated balloon therapy is associated with superior anti-restenosis efficacy compared to uncoated balloon angioplasty, and there was no evidence of any increased safety issues.

With the increase in the use of DCBs, we are quickly learning about the limitations of this technology. First, only one drug (paclitaxel) and one dose (2–3 μg/mm²) are available for all clinical situations. DCBs come in fixed balloon sizes (length and diameter); a multitude of devices must be kept on stock to address the various anatomical presentations, and it may be difficult to precisely match the balloon to the lesion. For long or segmental lesions, and in tapered vessels, multiple DCBs may be required, which will significantly increase procedural costs. In addition, in currently marketed DCBs, at least 80% of the drug is released to the systemic circulation, further adding concern to the use of multiple devices. In tortuous or otherwise difficult vascular anatomy, questions regarding loss of drug and coating during transit to the target site remain unanswered, as well as uncertainty concerning long-term systemic effects of the various coatings. These and other questions have led to an extended and uncertain regulatory pathway in the United States; in the U.S., there currently are no FDA-approved DCBs, and it is not certain when we will see the first one.

Fluid drug delivery vs. DCBs

In the United States, without the availability of any DCB, perhaps we have to look back to the Greek philosopher Plato, who advised us that “Necessity is the mother of invention”, and find a “solution” using the “Old Way” of fluid drug delivery. We know that the mechanism of balloon angioplasty involves fracture of the plaque, followed by stretching of the vessel wall to effect lumen expansion. Thus, it is common to observe cracks, flaps, tears, and dissections at the angioplasty site. Such cracks, flaps, tears, and dissections provide direct access for fluidly-delivered drugs to reach the injured vessel wall. Balloons, on the other hand, will “tack up” a dissection, and if there is a large plaque burden or excessive calcium at the treatment site, efficacy of drug delivery by a balloon-based device may be diminished. Furthermore, drug delivery by a DCB requires contact between the device and the luminal wall. Optical coherence tomography (OCT) has confirmed that vascular intervention frequently results in an irregular lumen with a disrupted luminal wall. As illustrated in Figure 1, even when the plaque disruption is “controlled” by using, for example, focal force angioplasty techniques, one can envision incidences where a DCB may not make contact with the areas really in need of the drug. On the other hand, with fluid delivery, drugs can easily enter and go where they are needed.

Proponents of DCBs — and opponents of fluid delivery of paclitaxel — in vascular intervention frequently refer to the THUNDER Trial. THUNDER was the first randomized study that showed efficacy of a paclitaxel-coated balloon (Paccocath) to reduce restenosis following angioplasty in peripheral arterial disease. Like other DCB randomized trials, THUNDER compared the DCB to an uncoated angioplasty balloon. However, THUNDER also included...
a third arm in the study that comprised an intra-arterial infusion of paclitaxel mixed with contrast. The primary endpoint of the study was late lumen loss (LLL) at 6 months, and secondary endpoints included binary restenosis and target lesion revascularization (TLR). All three of these major endpoints were statistically significantly lower in the cohort treated with the Paccocath Catheter compared to the other 2 groups, and there were no statistical differences between the uncoated balloon and intra-arterial infusion groups. There is no argument that the paclitaxel-coated balloon was superior to the uncoated balloon in the THUNDER Trial. However, with respect to the intra-arterial infusion group (IA), if one reads the actual article that was published in the New England Journal of Medicine, and not simply look at the slides presented at the various vascular meetings, perhaps some of the “thunder” in the study will not be as loud. It appeared that patients in the IA group were supposed to receive a dose of paclitaxel equivalent to that provided by the DCB. However, while the systemic dosages may have been similar between the 2 groups, the actual dose delivered to the target vascular segment was significantly less in the IA group. The dose of paclitaxel on the DCB was 3 μg/mm². This dose was held at the lesion for one minute. Almost all of the drug was released from the balloon, and the amount of paclitaxel delivered systemically to these patients ranged from 1-17 mg (the amount depended on the balloon size, and number of DCBs used); the mean ± SD in the DCB group was 4.7±3.5mg. In the IA arm, 100 mL of the contrast media to be used in the procedure was replaced with 100ml of a paclitaxel-contrast solution having a paclitaxel concentration of 0.17 mg/mL. If during the procedure all of this solution was infused, the procedure would continue using plain contrast media, and thus patients in the IA group would receive a systemic dose up to 17mg of paclitaxel. Virtually all of the patients in this group received this maximum dose (mean ± SD was 16.8±1.9 mg). Unlike the DCB group, where the balloon occluded blood flow and the 3 μg/mm² dose of paclitaxel was held at the dilated lesion for one minute (an equivalent volumetric concentration is on the order of 3 mg/cc), in the IA group, blood flow was immediate after infusion (of the significantly lower paclitaxel concentration), and washed the drug away from the target site. Moreover, use of the paclitaxel-loaded contrast media began once the lesion was crossed with the guidewire, and so the drug infusion in the IA group began before plaque disruption by the angioplasty balloon; drug delivery with the DCBs occurred during balloon angioplasty. Experimental studies have suggested that paclitaxel uptake in the tissue is increased with vascular injury, such as that produced by balloon angioplasty. Thus, it was no surprise that the outcome for patients in the IA group did not differ from those in the uncoated balloon control group. Prevention of neointimal proliferation and reduced restenosis by fluid delivery of paclitaxel has been reported in clinical applications where blood flow is temporarily occluded, and the drug is allowed to remain in the target segment for a fixed period. In these cases, the Genie Catheter™ (Acrostak, Winterthur Switzerland) was used to provide local vascular delivery of fluid paclitaxel. The Genie Catheter (Figure 2) has a single balloon with enlarged proximal and distal portions that provide an occlusive function. The balloon is inflated with the diagnostic or therapeutic agent at a pressure of 2 atm, and small holes in the distal portion of the balloon allows the agent to fill the area between the enlarged portions. In a prospective randomized trial comparing local delivery of fluid paclitaxel after bare metal stent implantation (Group I) with bare metal stent implantation (Group II) and implantation of a commercial paclitaxel DES (Group III), the local paclitaxel delivery group (Group I) had significantly
Figure 4.—A 79-year-old male presented with rest pain in the left leg, and a history of diabetes, hypertension and smoking. A single TAPAS Catheter delivered paclitaxel to 3 discrete segments of the left superficial femoral artery following atherectomy. Paclitaxel was mixed with a 50% solution of contrast media and saline to a final drug concentration of 3 mg/mL. Drug dwell time at each segment was 1 minute. After each infusion, the paclitaxel was aspirated from the vessel. Courtesy of Dr. Luigi Steffanon, Hesperia Hospital, Modena, Italy.
Targeted fluid drug delivery —

The TAPAS® catheter

The TAPAS® catheter (ThermopeutiX®, Inc., San Diego, CA, USA) is a new device, recently receiving FDA clearance in the US and the CE mark in Europe, that provides efficient, safe, and cost-effective drug delivery in the peripheral vasculature. As shown in Figure 3, TAPAS® (“Targeted Adjustable Pharmaceutical Administration System”), features two very-low-pressure compliant occlusion balloons that enable targeted local delivery of any physician-specified agent. The distance between the balloons defines the treatment zone, and a coaxial design allows this distance to be adjusted repeatedly during the procedure from 15 mm to 300 mm to allow treatment of long vessels with only one device. The ability to adjust the length of the treatment zone and greatly extend the length, is a significant advantage, and allows for a safe, effective, and more economical treatment of long diffuse disease, which is common in PAD. Unlike other devices, such as DCBs and the Genie Catheter, the drug can be aspirated out of the catheter after treatment. This allows treatment of multiple vascular segments without releasing an excessive systemic drug dose to the patient. The ability to treat several vascular sites with a single device during the procedure relates to additional cost savings.

With TAPAS®, drug selection and dose to the treatment site are at the discretion of the physician, and this provides for a variety of clinical applications with a single device. In a post-market surveillance analysis conducted by the manufacturer, ThermopeutiX, Inc. (87 cases), 9 drugs in 5 different clinical applications were reportedly used with the TAPAS® catheter. These applications included thrombus management (glycoprotein IIb/IIIa inhibitors and lytics), sclerotherapy (Atossisclerol), prostrate cancer (Abraxane), and restenosis prevention (paclitaxel and tacrolimus). Three exemplary cases are shown in Figures 4-6. In more than half of the cases, TAPAS®

![Figure 5](image)

Figure 5.—A single TAPAS® catheter delivers a solution of Atossisclerol 2% in contrast media to two target sites in a spermatic vein. A) TAPAS® was positioned at the first site (7 cm) in the spermatic vein from a femoral vein access; B) the sclerosant and contrast media is introduced to the first target site; C) after removing the drug from the first site, the TAPAS® catheter is repositioned at the second treatment site (15 cm). Drug dwell time at each segment was 3.5 minutes. Courtesy of Dr. Paolo Gazzo, Hospital Santa Corona, Pietra Ligure, Savona, Italy.
was used to locally deliver paclitaxel to reduce restenosis following peripheral vascular intervention. Vessel diameters ranged between 4-6 mm, and lesion lengths of 50-450 mm were treated. Dwell time was 2-5 minutes. Paclitaxel dosages ranged from 1.2-3.0 mg/mL, and no drug-related adverse effects were reported. The “exact,” or “ideal” paclitaxel dosage has not been established, but perhaps this may not be that important. Clinical studies of DCBs with paclitaxel dosages of 2 μg/mm² and 3 μg/mm² report similar results. In a porcine model, Shishehbor delivered 3 concentrations of paclitaxel (0.67, 1.2 and 2 mg/mL) with a TAPAS® catheter at dwell times of 2 and 5 minutes, and found little difference in the amount of tissue uptake. Because of the number of positive clinical studies of DCBs, many of the TAPAS® users begin with a “starting dose” similar to the DCB. To have a paclitaxel dose acting at the luminal wall that is comparable to that of the commercially available DCBs, it is more or less a question of geometry. The DCB dose is specified by a surface area of the balloon, and is either 2 μg/mm² or 3 μg/mm². For fluid delivery into a cylindrical vessel segment, we would “revolve” the surface area of the vessel wall (equivalent to the DCB surface area) into the volume of the cylinder. So, the equivalent concentration of the paclitaxel to be infused is 2 or 3 μg/mm³. For a more convenient unit of measurement, one can convert cubic millimeters to cubic centimeters (“cc’s”) by multiplying by 1000, end up with a paclitaxel concentration or “dosage” of 2 or 3 mg/cc. For a given concentration, the amount of paclitaxel delivered to the vessel is a function of the volume of the target treatment zone; for DCBs, the amount is related to the surface area of the balloon. Table I compares the amounts of paclitaxel delivered to various vessel segments by a 3 μg/mm² DCB and TAPAS® infusing paclitaxel at concentrations from 0.6-3 mg/cc. Note that in a 4 mm vessel, a 3 mg/cc dose will deliver the same quantity of paclitaxel as the DCB, but in a 6 mm vessel, the 2 mg/cc dose will be equivalent. Although both TAPAS® and the DCB can deliver equivalent amounts of paclitaxel, most of the drug may be removed after treatment with TAPAS®, whereas most of the DCB-delivered paclitaxel will remain the patient. In addition, TAPAS® has a much longer treatment zone than the currently marketed (outside the USA) paclitaxel-coated balloon catheters; with the DCBs, multiple catheters would need to be employed to treat vessel segments longer than the longest available balloon length. The ability of a single TAPAS® to treat longer vessel segments may provide a risk reduction by avoiding multiple DCB manipulations and positioning, which could result in under- and/or overdosing target vessel segments (“geographical miss” or overlap, respectively). The “recipe” to mix paclitaxel for delivery by TAPAS® is quite straight-forward. Commercially available paclitaxel comes standard in a concentration of 6 mg/ml. A typical bottle contains 5 mL, and thus has 30 mg of paclitaxel. We recommend mixing the paclitaxel with contrast media so that the infusion can be seen on fluoroscopy, and also, paclitaxel mix-
National registries are invaluable in monitoring interventional vascular medicine therapy, on-going clinical trials continue to provide evidence of the safety and effectiveness of drug-coated balloons. However, as with any emerging technology, regulatory issues are a growing concern, and some of these devices and procedures are not yet available in the United States. Economic pressures and increased regulation continue to challenge innovation and the way we treat our patients, but an unassuming technique of simply infusing drugs may just save the day. The drug-coated balloon is quite a remarkable innovation. However, except for the relatively few patients who get enrolled in a clinical trial, this therapy is not available in the United States, and it is not very clear when the first DCB will be approved by the FDA. The costs to develop these devices and clear regulatory hurdles are staggering, and by the time they indeed enter the US market, perhaps the question may be, “Can we afford them?”

Targeted fluid drug delivery is here to-day, and because of its value proposition, it is here to stay. Consider that a single TAPAS® catheter can be used to deliver multiple assorted drugs at multiple different sites in the same patient in the same setting. This should significantly reduce costs compared to the single-drug, single-dose, single-size and single-use drug-coated balloon.

In addition to providing care to our patients today, targeted drug delivery devices can help bring about discovery of new therapies for tomorrow. With its simple, but unique features, the TAPAS® catheter

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**Table 1.** Amount of paclitaxel in various vessel segments.

Future directions with the “old way” of drug delivery

With the new mantra in interventional vascular medicine to “leave nothing behind,” and the introduction of simple, but effective delivery devices like the TAPAS® catheter, we see a path “back to the future” with fluid drug delivery. Economic pressures and increased regulation continue to challenge innovation and the way we treat our patients, but an unassuming technique of simply infusing drugs may just save the day. The drug-coated balloon is quite a remarkable innovation. However, except for the relatively few patients who get enrolled in a clinical trial, this therapy is not available in the United States, and it is not very clear when the first DCB will be approved by the FDA. The costs to develop these devices and clear regulatory hurdles are staggering, and by the time they indeed enter the US market, perhaps the question may be, “Can we afford them?” Targeted fluid drug delivery is here today, and because of its value proposition, it is here to stay. Consider that a single TAPAS® catheter can be used to deliver multiple assorted drugs at multiple different sites in the same patient in the same setting. This should significantly reduce costs compared to the single-drug, single-dose, single-size and single-use drug-coated balloon.
may be used as a tool to facilitate and expedite the investigation of new drugs, dosages, applications and drug combinations. Unlike drug eluting devices, by separating the drug from the device, the safety and efficacy of the drug, dose and/or drug combinations may be studied without the distractions of the drug-device interaction. For example, in vascular medicine we have been on a quest to resolve the issue of restenosis ever since Andreas Grünitzig inflated his first balloon in an artery. In our journey, we went from device to drug to drug/device combo. With DES, the drugs worked so well to prevent tissue growth, a new problem was created — the risk of late thrombosis associated with a lack of tissue covering the bare stent struts. It took years and countless dollars to sort out this problem with long-term dual antiplatelet therapy (DAPT) — a drug solution. The quest now resumes with bioabsorbent stents and drug-coated balloons, hoping to maintain the long-term anti-restenosis benefit and reduce the long-term DAPT need. Are we chasing our tails? With the lengthy time and expense of developing safe and effective coatings and bioabsorbable matrices, the efforts remain to be focused on a single drug and dose, trying to find a “one size fits all therapy.” Perhaps we are being misdirected, and are not asking the right questions. Each of our patients are different, some have diabetes, some present with in-stent restenosis, and we all have our “frequent flyers,” who come back to the cath lab every few months. Perhaps it is only a question of finding the right dose to match the indication; in many aspects of medicine, drugs are titrated to the specific conditions of the patient. Why do we act differently in treating vascular disease? Why do we continue to try to treat restenosis with a single drug? From years of research, we know that restenosis is a multi-faceted process that includes inflammation, platelet aggregation, smooth muscle cell proliferation and other processes, and yet, with our DES and DCBs we only treat the proliferation. Perhaps the answer lies in a combination of drugs. Targeted fluid drug delivery, especially with the ability to aspirate the drug out of the body after treatment, provides the means to examine efficacy without confounding variables in a much safer manner. Like its gastronomical namesake, with TAPAS®, we can “try a little of this, try a little of that”, and more rapidly begin to understand the questions that will lead us to the answers we seek. Perhaps DES, or even DCBs, with their singular approach have become the “Old Ways” to locally deliver drugs, and, with tools like TAPAS®, it will be a “New Day” for targeted drug delivery.

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