

EDITORIAL

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Drug-eluting balloons: where are we and what are the problems?

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The starting point of percutaneous transluminal coronary angioplasty was defined by Andreas Grüntzig in 1977 [1]. He developed the novel technique of revascularization and established a new speciality – interventional cardiology.

Since that time, interventionalists have been confronted with the problems of vessel recoil during the procedure and restenosis within the first 6 months of balloon angioplasty. In spite of progress in some indications, in others these challenges have lost nothing of their significance, motivating investigators to pursue their research efforts with a view to finding new strategies for overcoming these difficulties.

Stents proved to be a significant advance in reducing the frequency of restenosis by eliminating elastic recoil and negative remodeling at the treatment site [2]. However, neointimal proliferation is not prevented by stenting, and thus in-stent restenosis became a ‘new’ disease, especially in some patient populations such as diabetics or in certain lesions such as bifurcation, long lesions, lesions in small vessels, total occlusions and diffuse disease [3]. The systemic administration of anti-inflammatory, antiproliferative, anticlotting or other agents before or after balloon dilatation was shown to effectively reduce neointimal hyperplasia in animal models. Clinical use in humans, however, failed to result in adequate restenosis prevention [4].

The advent of drug-eluting stents (DESs) marked a decisive advance, enabling direct transfer of drugs to the target site and prolonged exposure of the vessel wall. Sirolimus and paclitaxel were shown to be effective pharmacological inhibitors of neointimal hyperplasia *in vitro* and *in vivo* [5,6]. Stents coated with these agents were successfully used in both the coronary arteries [7] and below the knee [8]. By contrast, use of these stents were not found to be superior to bare-metal stents in femoral and popliteal arteries or in patients with severe diffuse disease and long, complicated lesions [9]. The occurrence of late stent thrombosis, caused by incomplete endothelialization of the stent struts and an inflammatory response to the polymer matrix, considerably limited the use of DES [10,11].

Coating paclitaxel onto the surface of conventional percutaneous transluminal coronary angioplasty balloon catheters with a new coating technique that provides immediate drug release upon inflation was a new approach to preventing restenosis without having to implant a stent. The drug is transferred to the dilated segment when the balloon is inflated. An effective local drug concentration is achieved with very low systemic exposure.

Paclitaxel admixed to a small amount of the hydrophilic x-ray contrast medium iopromide (Ultravist®) emerged as a very effective coating matrix from numerous *in vitro* and *in vivo* experiments investigating different coating techniques, the adhesion of paclitaxel to the balloon surface while the catheter is advanced to the lesion, and the release of the active agent into the vessel wall during balloon expansion [12,13]. Balloon catheters coated in this way have a paclitaxel dose of 3 µg/mm² of balloon surface and are marketed as Paccocath® (Bayer Schering Pharma AG, Germany).

Randomized clinical trials versus uncoated balloon catheters confirmed the effectiveness of Paccocath balloons in the treatment of in-stent restenosis of the coronary arteries (in-stent restenosis study [ISR]) and in the inhibition of restenosis in femoral and popliteal arteries (Thunder and Femoral-Paclitaxel [FEMPAC] studies) [14–16].

Since the initial research undertaken by Scheller *et al.*, several companies have started commercializing or developing drug-coated balloons (DCBs). Paclitaxel is currently the drug of choice due to tried and tested ability to reduce restenosis rates in coronary and peripheral artery disease, with the typical dose being 3 µg/mm² of balloon surface. The number of published trials and patients treated is still limited. Obviously, the way in which paclitaxel is formulated is important since some balloon catheters coated with the same or a similar dose of paclitaxel failed to show efficacy in animal experiments and clinical trials [17].

Why is this?

Various obstacles have to be overcome before the active agent can exert its beneficial effect at the site of an arterial lesion:

- The amount of drug on the balloon surface must be large enough and it must be dissolved in a solvent, possibly with an additive that forms a matrix on the balloon surface;
- The coating must ensure adequate adherence of the drug during manipulation of the catheter, insertion into the artery and catheter advancement through the blood stream;
- Enough of the agent must be present on the balloon at the lesion site to ensure transfer of an effective dose to the vessel wall during the short time of balloon inflation.

To overcome these obstacles, developers of DCBs must reconcile two conflicting aims: on the one hand, a loose coating may result in a release of particles before the target site is reached; if too much of the active agent is lost during passage through the blood stream, the concentration at the target site may be too low to be effective.

On the other hand, when the coating is firm and stable, largely preventing loss of drug during manipulations before the balloon reaches the target site, there is the risk that not enough of the agent may be transferred to the vessel wall at the site of the lesion during the short time of balloon inflation. In this case, the amount of drug delivered to the lesion might be too small for effective inhibition of restenosis.

Surprisingly, very good clinical results were achieved with the slightly irregular Paccocath coating and SeQuent® Please balloons, which have a coating based on a similar principle (paclitaxel with addition of Ultravist; B. Braun Vascular Systems, Germany) [14–16,18]. Good results were reported for FreePac™ paclitaxel-coated balloon catheters (Invatec, SPA, Italy) [19,20]. FreePac is a proprietary hydrophilic coating formulation with urea as a matrix substance.

A variety of other coatings are used by other manufacturers of DCBs. For instance, the second-generation DIOR® balloon (Eurocor GmbH, Germany) is a coronary-dilation balloon for human use, on which paclitaxel is mixed 1:1 with shellac, which is composed of a mixture of hydroxy fatty-acid esters and sesquiterpene-acid esters with a molecular weight of approximately 1000. The Lutonix catheters (Lutonix, Inc., USA) are coated with paclitaxel in an unknown matrix. Pantera Lux® (Biotronik AG, Germany) uses butyryl-trihexyl citrate as a carrier for paclitaxel. Butyryl-trihexyl citrate is used in different medical devices and cosmetics and is approved for blood contact in blood bags. The current version of Elutax® (Aachen Resonance, Germany) uses paclitaxel directly coated on the balloon surface without a matrix.

In November 2010, Blue Medical (The Netherlands) announced that the company received CE Mark approval in Europe for a paclitaxel-coated balloon, PROTEGE®, and simultaneously for PIONEER®, a coronary cobalt-chromium stent mounted on a paclitaxel-coated balloon, for the treatment of coronary diseases. Premounted bare-metal stents on DCBs may offer the advantages of stenting while avoiding the use of polymers and sustained drug release. Ideally, this may allow a shorter duration of dual antiplatelet therapy. However, in view of the less than optimal results of the PEPCAD Phase III randomized trial comparing SeQuent Please with premounted bare metal stents and Cypher® stents [21], clinical trials are mandatory before recommending this approach.

The current discussion on coronary applications of DCBs is based on several hundreds of coronary artery patients examined in clinical trials and the experience with marketed products. Although the use of DCBs appears to hold promise as a viable alternative to stand-alone balloon angioplasty and stent implantation for treatment of coronary and peripheral arterial disease [22], the place that such a system will find in the treatment of the multitude of clinical problems addressable by vascular interventions remains to be seen. In *de novo* lesions of coronary arteries, DCBs cannot replace drug-eluting stents because of recoil and dissections. A potential benefit is the reduced need for stents in complicated lesions. A strategy of DCB angioplasty with provisional spot-stenting in the case of severe

dissections may become a better alternative in long and complex lesions, bifurcations or in patients with contraindications to drug-eluting stents.

The available data on DCB angioplasty also clearly show that it is not the active agent alone that determines how effectively restenosis is prevented. It is the formulation of the coating as a whole that makes the difference between success and failure.

Developments over the last decades have shown that it is difficult to appraise the value of new techniques. Improvements are desirable with regard to more reliable adherence of the drug during production, mounting of stents and handling, while providing fast and complete drug delivery during the short time of balloon inflation. Experimental studies should investigate aspects on which data are still limited, such as the loss of drug during blood passage, drug release during balloon inflation, uptake of the drug into tissue and the effectiveness in animal models. Preclinical investigations cannot replace large randomized studies but provide useful initial insights into possible success or failure, and they

are not very time consuming. Conversely, it takes a long time before the results of large, representative studies with several treatment arms and possible repeated angiographic follow-up are available. The difference between the coronary arteries, bypass grafts, peripheral vessels above the knee or below the knee, dialysis shunts, intracerebral vessels and so forth, and the range of clinical conditions of the patients treated, will continue to give rise to controversies and discrepancies between preclinical and clinical results.

Financial & competing interests disclosure

Bruno Scheller and Ulrich Speck are coinventors of a patent application by Charité University Hospital, Berlin. Beatrix Schnorr is an employee of Charité, which licensed the patent to various companies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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