FEATURED EDITORIAL

Prevention of restenosis: is angioplasty the answer?

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"The drug-coated balloon has the potential to improve the limited results of drug-eluting stents"

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Numerous, initially promising, approaches using systemic antiproliferative agents have so far failed to prevent restenosis after percutaneous coronary interventions.¹ Thus, restenosis prevention continues to be a challenge to interventional cardiology. Some years ago, intracoronary radiation therapy was considered a breakthrough treatment against in-stent restenosis,² but the method crucially relies on the availability of the radiotherapeutic armamentarium. Another major limitation of brachytherapy is late thrombosis, especially when combined with stent implantation.³

DRUG-ELUTING STENTS

Clinical trials on drug-eluting stents (DES), which suppress neointimal proliferation by the sustained release of antiproliferative drugs, have shown excellent results in reducing restenosis.⁴⁻⁶ DES are well accepted in the prevention and treatment of coronary restenosis. The use of DES in the USA and other countries such as Switzerland is approaching 90% of all stents used. Meanwhile, concerns have been raised that such drug releasing stents, while being effective, may be associated with an increased incidence of late thrombotic complications⁷⁻⁹ or death.¹⁰

Sustained drug release seems to be essential for stent-based local drug delivery due to the inhomogeneous drug distribution from a DES to the arterial wall (fig 1).¹¹ About 85% of the stented vessel wall area is not covered by the stent struts, resulting in low tissue levels of the antiproliferative agent in these areas. Cell culture experiments indicate that low drug concentrations require much longer exposure times to achieve sufficient inhibition of cell proliferation compared with higher concentrations.¹² Therefore, high drug concentrations on the stent struts, including a controlled and sustained release mechanism, are mandatory for stent-based local drug delivery,¹³ resulting in delayed and incomplete endothelialisation of the stent struts. Autopsy studies show that even beyond 40 months DES are not always fully covered by endothelium.¹⁴ Furthermore, the polymeric matrixes on the stent embedding the antiproliferative drug could induce inflammation and thrombosis.^{15 16} On the other hand, incomplete suppression of neointimal hyperplasia at the stent margins or between the struts may limit the efficacy of DES.^{11 17}

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New concepts to overcome the limitations of DES should avoid a sustained drug release from stent struts to allow for earlier endothelialisation. There should be no use of polymers or other sustained release technology capable of inducing inflammation. Non-stent-based local delivery of antiproliferative drugs may offer additional flexibility and efficacy in the entire range of applications. It may allow for a homogenous drug distribution to the arterial wall.

Paclitaxel has been previously used in studies employing a variety of catheter-based local drug delivery approaches. Thus, "double-balloon" catheter,¹⁸ porous balloon catheter,¹² and even intrapericardial administration¹⁹ were utilised. Although all of these approaches showed efficacy in preclinical trials they required special devices, involving blockage of blood flow or additional vascular injury.

DRUG-COATED BALLOONS

The drug-eluting balloon (Paccocath) is a regular angioplasty balloon requiring no special handling. It is a novel option for the treatment of coronary and peripheral arteries. We performed our basic experiments leading to the development of this device after the surprising discovery that sustained drug release is not a precondition for long lasting restenosis inhibition. Once exposed, cells retained paclitaxel in vivo for 6 days even if plasma levels were far below the detection limit.²⁰ Preclinical studies have shown that brief contact between vascular smooth muscle cells and antiproliferative drugs can result in prolonged inhibition of neointimal proliferation.²¹⁻²⁴ Initial drug concentration as achieved by the drug-eluting balloon is a substitute for sustained release. The drug is administered only during the short inflation time of the balloon, and is subject to rapid dilution and elimination. Endothelial cells and their precursor cells migrate to the injured vessel segment.^{25 26} Re-endothelialisation should not be inhibited because these cells entering the lesion from distant locations had no previous exposure to the drug and, therefore, maintain their capability to proliferate (fig 2). The innovative coating technique of balloons enables a controlled dose of paclitaxel to be released during dilatation, as soon as the balloon is inflated inside the stenotic artery.²³ To our knowledge, drug-coated balloons are currently the most advanced and possibly superior alternative to stent-based local drug delivery.

The Paccocath ISR trial was a controlled, randomised, blinded, first-in-man study that investigated the use of paclitaxel-coated balloon catheters for treatment of coronary in-stent restenosis. Patients who were treated with the coated

Figure 1 Inhomogeneous drug distribution from luminal surface after implantation of a drug-eluting stent (DES) (reprinted with permission from Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. *Circulation* 2001;104:600–5).¹¹ Homogeneous drug distribution from luminal surface after an inflation of 60 s with a drug-coated balloon (porcine coronary artery, experiments done by Nicola Kaufels, Berlin, Germany).

Figure 2 Complete endothelialisation of a CoCr stent (Coroflex Blue, BBraun vascular systems, Berlin, Germany) implanted with a drug-coated balloon with 3 µg paclitaxel/mm² balloon surface 5 days after implantation. Von Willebrand staining. Porcine coronary model.

balloon had significantly better angiographic results and concomitant improvement in 12-month clinical outcomes compared with patients treated with an uncoated balloon. The mean (SD) in-segment luminal loss was reduced from 0.74 (0.86) mm in the uncoated balloon group to 0.03 (0.48) mm in the coated balloon group ($p = 0.002$) (fig 3). There were no coating-related adverse events. Clopidogrel was given for only 4 weeks in both groups.²⁷ Further clinical studies in different indications are underway.

In perspective, the drug-coated balloon has the potential to improve the limited results of DES—for example, in patients with coronary in-stent restenosis, in bifurcations, in small vessels, or in other circumstances where stent implantation is not desirable or possible. With the drug-coated balloon there is no need for a stent. However, the combination with modern, flexible, thin bare metal stents is another promising application. The treatment of peripheral arteries, where DES have shown limited efficacy, may become a future domain of the coated balloon.

Figure 3 Late lumen loss in-segment after treatment of coronary in-stent restenosis. Comparison of conventional balloon angioplasty, implantation of a Taxus stent, Cypher stent, and angioplasty with the drug-coated balloon (Paccocath). Data from the Paccocath ISR I trial (conventional angioplasty and Paccocath)²⁷ and the ISAR-DESIRE study (Taxus stent and Cypher stent).²⁸

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Conflict of interest: Dr Speck and Dr Scheller report being co-inventors on a patent application for various methods of inhibiting restenosis, which was submitted by Charité University Hospital in Berlin. Dr Speck reports serving as consultants to Schering AG, Berlin

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IMAGES IN CARDIOLOGY

A case of surgical treatment of severe high blood pressure in an adult

A 24-year-old man, asymptomatic, was referred for a diagnosis of high blood pressure (190/100 mm Hg). Pulses in the femoral arteries were weak, and the blood pressure was astonishingly low in the inferior limbs (80/40 mm Hg).

Transthoracic echocardiography confirmed the findings of the electrocardiogram. There was left ventricular hypertrophy, but also an aspect of coarctation with very high velocities in the aortic isthmus (>2.5 m/s). This was confirmed by transoesophageal echography and by computed tomographic angiography, with three-dimensional reconstruction showing complete interruption at the aortic isthmus with aortic arch hypoplasia and a large number of developed collateral arteries (panel A).

A surgical treatment was performed for severe high blood pressure despite pharmacological treatments in a young adult.

A median sternotomy was performed, associated with a left thoracotomy in the fourth intercostal space to expose the descending thoracic aorta. Firstly, to preserve the intercostal arteries (>0.6 cm diameter), the distal end of the Dacron graft was sewn laterally on the descending aorta. Under deep hypothermia and circulatory arrest, we then patched the arch hypoplasia with the proximal end of

Angiographic computed scan was performed 10 days after and showed a good permeability of the aortic graft and preserved collateral arteries.

One month later, the patient is doing well and the blood pressure has stabilised at around 110/60 mm Hg. The only treatment is aspirin 75 mg/day and bisoprolol 10 mg/day.

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