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REGULAR ARTICLE

Local catheter-based delivery of antithrombotic or antiproliferative drugs: A new concept for prevention of restenosis

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Abstract

Background: Drug eluting stents have reduced the incidence of restenosis after percutaneous coronary interventions significantly, but cause concern about long term safety. Local drug delivery using special application catheters is an alternative approach for intracoronary pharmacotherapy. Besides the fact, that no problematic coating as drug carrier has to be used, a local delivery independent of the stent itself by using catheter techniques offers further advantages – such as the possibility to treat the whole vessel wall, stent edges and adjacent vessel segments and not only the area close to the stent struts.
Methods and Results: We have developed a new local catheter-based delivery system for local intracoronary pharmacotherapy. An antithrombotic as well as an antiproliferative therapy concept for prevention of restenosis are presented in the manuscript. Our data show that local drug delivery of platelet glycoprotein VI and paclitaxel were effective in the reduction of thrombus formation and neointima formation in experimental animal models.
Conclusions: A combination of early antithrombotic and antiatherosclerotic mechanisms may be a realistic and effective approach to minimize postinterventional thromboischemic events and neointima formation. These results may contribute to an advanced and even combined local intracoronary pharmacotherapy in near future, independent of stent coatings.

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More than 1.5 million percutaneous transluminal coronary angioplasty procedures (PTCA) are being performed worldwide each year [1]. Since coronary artery disease is the leading cause of death in the western world, our population is constantly aging and medical progress is unbowed, this number will grow without doubt.

A still unresolved problem of this procedure, however, is the renarrowing of primarily successful dilated vascular stenoses, called restenosis. Restenosis is the main limitation of PTCA, occurring in 20–50% of all cases. Although the introduction of stents reduced the percentage of restenosis to a limited extent, the clinical problem still exists. Restenosis in stents is even more difficult to treat than was restenosis before [2,3]. Drug eluting stents (DES), which release an antiproliferative compound from a stent coating, have reduced the incidence of in-stent-restenosis dramatically by pharmacological inhibition of neointima formation. Since their approval in 2003, DES have revolutionized the practice of interventional cardiology [4]. Currently, more than 85% of all coronary interventions are performed with DES in the United States, while European countries follow a more conservative approach. However, the initial enthusiasm (0% restenosis) was premature, in the "real world of coronary intervention", aside of clinical studies, restenosis still exists. Furthermore there is serious safety concern with DES. The coating of the stent struts, mostly a polymer, is potentially thrombogenic and causes inflammatory reactions. The drug concentration is highest at the stent struts, where healing is most important, whereas the areas between the struts and at stent margins are not covered. This may lead to incomplete suppression of neointima formation and limit the efficacy of DES [5–7].

Only recently, several reports of late in-stent thrombosis more than 1 year after DES implantation were published, which gives reason for additional concern [8,9].

We chose a new concept of intracoronary delivery of an active substance via application catheters after implantation of a bare metal stent. The main advantage of this concept is the fact, that no problematic coating as drug carrier has to be used but offers also further advantages – such as the possibility to treat the whole vessel wall and not only the area around the stent struts. Even more importantly, the stent edges and adjacent vessel segments can be covered by pharmacotherapy to avoid the so called "edge-effect" of drug eluting stents.

Thus the basic idea behind this technique was to see drug and application as a whole and to find a customized solution that accounts for both aspects of intracoronary therapy.

Since our research group was among the first worldwide to evaluate the potential of paclitaxel for restenosis prevention, a short overview of the data from our in vitro and in vivo experiments will be given in one part of the manuscript. The other part of this article deals with a different but maybe synergistic approach for restenosis prevention: the local intracoronary inhibition of platelet adhesion to exposed extracellular matrix proteins, which represents the first response to vascular injury, in an attempt to interfere as early as possible in the onset and progression of pathological arterial thrombosis. Since GPVI is critically involved in platelet-mediated arterial thrombosis, this makes the receptor a promising target for antiplatelet treatment [11–13]. The hypothesis for the following experiments was that a local catheter-based application of GPVI to injured, collagen-exposing vessels would prevent thrombus formation in vivo.

Catheter-based local drug delivery

Catheter-based local drug delivery for prevention of restenosis was invented before stent implantation became a routine method in percutaneous coronary intervention. The main reason for this, besides the apparent species differences, was the fact that a 10–70 fold higher dose was used in animal experiments compared to the use in humans [14,15]. To date, possible severe side effects and a locally insufficient amount of drug concentrations limit the systemic medical approach to improve the long term efficiency of PTCA. Therefore, interest has recently focused on local administration of potentially effective drugs directly to the site of arterial injury following coronary angioplasty [14–18]. In order to perform local drug delivery, porous balloon catheters were developed, instruments consisting of a normal balloon with laser-drilled holes that allow the flow of infusate through the application pores when the balloon is inflated [19]. A number of studies have documented so far that it is possible to deliver different drugs locally into the vessel wall using a porous balloon device, but since high injection pressures up to 10 atm were used in several of these early studies to obtain high intramural drug concentrations, considerable additional vascular injury was observed as the major disadvantage of this device [14–19]. Several potentially less traumatic catheter systems for local drug delivery were investigated, such as double balloons, balloons coated with a thin layer of drug-absorbing-polymer or balloons with a microporous design [20]. However, the physical spectrum of applying drugs via catheters is limited to a spectrum between