Drug-eluting balloons for percutaneous coronary interventions

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The simple and originally naïve idea of dilating a coronary stenosis to restore unobstructed coronary flow through percutaneous transluminal coronary angioplasty (PTCA) (1) has been a major advance in the treatment of acute coronary syndromes and is currently also commonly used in stable coronary artery disease (2). However, there is no such thing as a “free lunch”, and the vascular injury caused by the balloon-induced barotrauma elicits an initial inflammatory response in the vessel wall that leads to vessel restenosis in 30–40% of cases through two major processes: a) negative vascular remodeling (used to designate late vessel shrinking after the acute dilation) and b) cellular proliferation. While the former is abolished by the use of stents, acting as metal scaffolds, such metal devices themselves actually increase the risk of the latter, leading to neointimal hyperplasia often more severe than when the plain “old” balloon angioplasty was used (3). Interventions with balloon angioplasty and/or the use of stents are now unanimously referred to as percutaneous coronary interventions (PCI). Drug-eluting stents (DES) were seen as the final solution of the problem, since they dramatically reduce in-stent restenosis by inhibiting cellular proliferation (Fig. 1).

The initial enthusiasm for DES, however, has been recently tempered by the concern for the occurrence of late stent thrombosis (4), caused by an incomplete endothelialization of the stent struts and an inflammatory response to the polymer (5). We have therefore lately witnessed some revival for the use of bare-metal stents (BMS), which will be probably accompanied by a predictable re-increase in the rate of in-stent restenosis.

Because of this, there is currently uncertainty on the optimal selection of stents. As dual antplatelet therapy is recommended for at least 12 months after DES (6), patients at higher risk of bleeding (the elderly, patients with cancer, candidates to oral anticoagulant and to any type of surgery) or subjects with expected lack of adherence or inability to tolerate an extended course of dual antplatelet therapy are undoubtedly better candidates to receive BMS. On the other hand, most conditions are suited for this purpose because its lipophilic properties account for satisfactory penetration and persistence in the tissue; moreover, in the coating preparation, its solubility is enhanced by ad-
Figure 1: Mechanisms of lumen enlargement and restenosis after percutaneous coronary interventions (PCI). A coronary lesion (on the left) can be effectively treated with plain “old” balloon angioplasty (POBA) or stent-PCI, and both techniques obtain most of the gain with a stretching of the entire vessel, with POBA disrupting the plaque and frequently causing dissections. Angiographic restenosis occurs at a higher rate after POBA, due to vessel remodeling and cellular proliferation (grey area), and to a lower rate after bare-metal stents (BMS) (here only through the neointimal component). Such neointima formation is dramatically reduced by drug-eluting stents (DES). DES however also cause incomplete or delayed strut endothelization, which can be responsible for even late (>1 month) thrombosis and acute vessel occlusion.

showed a statistically significant increase in lumen diameter and luminal area and a corresponding decrease in maximum neointimal thickness and neointimal area in the vessels treated with PEB. Reduction in neointimal hyperplasia ranged between 57–61% and was comparable in all the PEB arms; inflammation scores were similar in treated groups, and significantly higher than controls. No edge effect was detected. A satisfactory endothelization was documented in all samples. Therefore, a short inflation time of a single balloon seems equally effective as multiple or prolonged inflations, which might be occasionally used in conditions at higher risk of recurrence of in-stent restenosis (e.g. diabetes or renal dysfunction). Higher local doses of paclitaxel also appeared well tolerated.

PEB reduces cellular proliferation inside the stent and seems in principle, therefore, extremely well suited for the treatment of in-stent restenosis (10). PEB angioplasty cannot be actually proposed as a stand-alone therapy for de novo coronary lesions, since paclitaxel effectively inhibits cellular proliferation, but does not reduce vascular recoil, which is a major component of post-balloon-only angioplasty restenosis. In-stent restenosis, conversely, is characterized by an extremely high rate of recurrence (30–80%) with traditional percutaneous treatments. Currently, the deployment of a DES inside the previous restenotic BMS is considered the best option for this subset of patients, and proved better than intravascular brachytherapy (12). However, a stent “sandwich” cannot be viewed as the ideal solution of this cumbersome problem because – as pointed out above – the local concentrations of the drug at variable distance from the stent struts are likely dishomogeneous, and also because such a solution is not optimal for treatment of bifurcation lesions.

In the search of the “ideal” device to restore coronary patency, fully bioabsorbable stents seem also extremely promising: they are able to acutely scaffold the artery, tackling dissections and counteracting vessel recoil, and later to “magically disappear” from the vascular wall. However, in the first-in-man experience, the four-month degradation of magnesium struts produced a late vessel recoil, and this translated into an unacceptable rate of 45% target-vessel revascularization at one year (13). More promising results were recently obtained with the first experience of a fully bioabsorbable everolimus-eluting stent (14), for which at one year the rate of major adverse cardiac events was 3.3%, with only one patient having a non-Q wave myocardial infarction. Neither target lesion revascularisations nor late stent thromboses were here recorded.

We must acknowledge the limited power of the present study to detect low frequency events, such as stent thrombosis, and therefore a final statement about safety cannot be given; this limitation is, however, common in preclinical studies. Endothelization, a possible surrogate for safety, was here documented to be uniform on the stent surface, without any evidence of platelets or fibrin deposition surrounding stent struts, which form the substrate underlying stent thrombosis in both animals and humans. We would wish to see many more studies like this meticulously testing PEB (and newer PCI devices in general) in a suitable animal model, and therefore welcome the device as an effective strategy for the treatment of in-stent restenosis. However, preclinical studies cannot be shortcuts for carefully performed clinical trials. The study presented here will likely be the solid background for one or more multicenter clinical trials testing the full therapeutic potential of PEB.
References