Stent Coatings – What Are the Real Differences?

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Summary

Since its introduction into clinical cardiology, several studies have shown the superiority of coronary stent implantation as compared to conventional balloon angioplasty. However, restenosis still remains a major drawback to this new technique. Basic research in animal models have identified stent-related factors such as the material and design as major determinants of the degree of intimal proliferation after stent implantation. In order to further improve stent performance the concept of stent coating has been developed. By using this approach favorable characteristics of different materials can be combined. Conceptually, passive coatings, which only serve as a barrier between the backbone material and the tissue, and active coatings, which directly interfere with the process of intimal proliferation, must be distinguished. Until now there were several passive coatings commercially available which provided good results in animal models and preliminary clinical studies. As any surface evokes some kind of tissue reaction which promotes the process of restenosis, active stent coatings with antiproliferative drugs have been proposed. Animal studies have also revealed convincing results in this field of stent coating. However, clinical studies not only showed active stent coatings to be effective in preventing restenosis, but also demonstrated potential limitations, such as subacute stent thrombosis. Due to the lack of large randomized studies using the coating technique, further studies will have to confirm the initially promising results before reliable recommendations can be made.

Key Words

Coronary stents, restenosis, in-stent stenosis, thrombogenicity

Introduction

In 1977, percutaneous transluminal coronary angioplasty (PTCA) was introduced into clinical practice by Andreas Gruentzig [1]. However, balloon angioplasty remained limited due to abrupt vessel closure that necessitated emergency bypass surgery in 2 to 3 % of patients, and restenosis that required repeat revascularization in 30 to 50 % of patients [2]. To overcome these major drawbacks of angioplasty the concept of using endovascular prostheses was proposed. In 1985, Sigwart et al. reported the successful implantation of stents in the coronary arteries of eight patients [3]. Since then several investigators showed that stent implantation is a safe treatment for acute or threatened vessel closure [4]. After these promising results in bail-out situations, indications for stenting have been expanded to include the treatment of de novo lesions. In 1994, two large trials demonstrated the superiority of stenting with respect to restenosis. Stent implantation

reduced the rate of restenosis by 30 % as compared to conventional angioplasty [5,6]. Despite these promising results, stents have not eliminated restenosis and in-stent stenosis remains a major clinical problem [7]. Following successful balloon angioplasty or stent implantation, endothelial repair processes are initiated which may contribute to restenosis in the treated vessel segment. Experimental evidence exists for five major mechanisms that promote restenosis after PTCA and stent implantation: 1) elastic recoil, 2) thrombus formation at the injury site, 3) inflammation, 4) proliferation of smooth muscle cells, and 5) excessive formation of an extracellular matrix (ECM). As elastic recoil is counteracted by stent implantation, this mechanism is of minor importance [8]. After stent implantation adhesion and formation of thrombocytes, aggregate at the stent struts and the injury site are observed. Consequently, thrombocyte-derived factors such as platelet derived growth factor (PDGF) serve as chemoattractants for smooth muscle cells, and stimulate the production of ECM [9]. Furthermore, stented vessels show reactive inflammatory infiltrates composed of lymphocytes, histiocytes and eosinophiles surrounding the stent wires [10]. It is assumed that this inflammatory reaction is a mixed response to vessel injury on the one hand, and non-specific activation mediated through metal ions released from the alloy of the stent, on the other hand. Cytokines released by inflammatory cells not only serve as smooth muscle mitogens, but also regulate the production of ECM [11]. Although the detailed mechanisms of inflammation are not completely understood, the correlation between the degree of inflammatory reaction and the extent of neointimal thickness suggests a central role for inflammation in the process of restenosis [12]. The laceration sites are invaded by spindle-shaped cells, most likely representing dedifferentiated smooth muscle cells [13]. Subsequently intimal hyperplasia is composed of the cellular elements mentioned above, and ECM consisting of collagen, elastin, and several types of glycoproteins [14]. Although it has long been assumed that cell proliferation is the major mechanism of intimal hyperplasia, Schwartz et al. have proposed that cells account for only about 11 % of neointimal volume, with the remaining volume consisting of ECM [15]. After neointimal formation, a redifferentiation of the spindle-shaped cells to α-actin-positive smooth muscle cells is observed [16]. The repair process is completed after 6 months with only minimal lumen loss occurring.

Rationale of Stent Coatings

There are three major stent-related factors influencing the degree of intimal proliferation:

- stent design, [17]
- stent material, [18]
- degree of vascular injury, [19].

Some materials exhibit excellent mechanical properties but have unfavorable biocompatibility, while other compounds with good biocompatibility won't produce viable stents. Therefore, stent coating is an approach that combines desirable characteristics of different materials. Using this approach, stent coatings can be applied as passive and active coatings. Whereas passive coatings serve just as barriers having good biocompatibility, active coatings should directly influence intimal proliferation. Active coatings are generally based on the effect of known drugs. These, in the true sense of the word active compounds, are either chemically bonded onto the surface of the stent or the drug is trapped in three-dimensional polymers which acts like a sponge.

Biodegradable Polymers

Biodegradable polymers were developed to improve stent biocompatibility per se, or to serve as a carrier for proliferation-modulating drugs. However, when van der Giessen and his colleagues studied five different biodegradable polymers [polyglycolic acid/polylactic acid (PGLA), polycaprolactone (PCL), polyhydroxybutyrate valerate (PHBV), polyorthoester (POE) and polyethyleneoxide/polybotylene terephthalate (PEO/PBTP)] in the porcine model, they determined that all of these compounds were associated with a significant inflammatory and proliferative response after 4 weeks [20]. These results suggest that biodegradable polymers per se do not lead to a reduction of neointimal proliferation. Therefore, an approach has been undertaken to formulate biodegradable polymers with drugs embedded in them during preparation. Drug dilution is achieved by disintegration of the biodegradable polymer portion of the stent. Through this approach several biodegradable polymers were found to be suitable carriers for antiproliferative drugs (Table 1).

Nonbiodegradable Polymers

There are many in-vivo animal trials investigating the biocompatibility of nonbiodegradable polymers [20].

Author	Bound compound	Polymer	Degradable	Model	Intima proliferation
	Animal studies				
Drachmann et al. [49]	Paclitaxel	Poly(lactide-co-Σ-caprolactone)	Yes	Rabbit	Reduction
Aggarwal et al. [50]	GP IIb/IIIa Receptor Ab	Cellulose	Yes	Rabbit	Equivocal
Lincoff et al. [51]	Dexamethason	Poly-l-lactid acid	Yes	Pig	Equivocal
Whelan et al. [52]	Phosphorycholine	Methacryloyl/laurylmethacrylate	No	Pig	Equivocal
Alt et al. [53]	Hirudin/Iloprost	Polylactid acid	Yes	Pig	Reduction
Yamawaki et al. [54]	Tyrosine kinase inhibitor	Poly-l-lactid	Yes	Pig	Reduction
De Scheerder et al. [55]	Heparin	Not described		Pig	Equivocal
Bei Ping et al. [56]	Methylprednisolone	Polyfluoroalkoxyphosphazene	No	Pig	Reduction
	Clinical studies				
Sousa et al. [26]	Sirolimus	Poly(ethyl methacrylate)/*n*-butylmethacrylate	No		Reduction

Table 1. Experimental studies with drug diluting.

These compounds have been examined as direct surface coatings and as carriers of biologically active compounds. When non-biodegradable matrices are used, drug delivery is achieved through sustained release of the drug by diffusion through the porous matrix. The most extensively investigated compounds with multiple medical applications are polyurethane, silicone and polyethylene terephthalate [21,22].

Polyurethanes are one of the most frequently used materials in industrial production being applied in the production of adhesives and foamed plastics. The chemical characteristics of these compounds are the urethane group (-NH-CO-O-). Animal studies in the rabbit model have shown that polyurethane-coated stents lead to an inflammatory cell response consisting of lymphocytic infiltration and foreign-body reaction with the appearance of multinucleated giant cells [23]. No effects have been demonstrated on the degree of intimal proliferation present after 28 days. These results demonstrate that a polyurethane coating per se does not significantly reduce the incidence of restenosis. Polyethylene terephthalate (Dacron) is a compound used in endoprostheses during vascular surgery. However, animal studies using this compound for vascular stenting revealed disappointing results with an increased incidence of restenosis [24].

Recently the nonerodable polymer poly(ethyl methacrylate)/n-butylmethacrylate (PEMBMA), which is predominantly used in orthopedic surgery, has been introduced in stent coating. Although this new bone cement has less toxic effects than conventional bone cement [poly(methyl methacrylate) (PMMA)], this compound also shows a marked cellular reaction when implanted in the paraspinal musculature of Sprague-Dawley rats [25]. This compound has been used as a carrier for the cell cycle regulator sirolimus. By using this approach promising results could be achieved with almost no restenosis [26]. Table 1 provides an overview on the biodegradable and nonbiodegradable polymers used as carriers for drugs [27].

Metallic Surface Coating

Gold belongs to the noble metals and its high biocompatibility makes it a suitable material to use in many medical implants [28,29]. It was found that coating 316L stainless steel with gold would ameliorate the biocompatibility of stents. In addition experimental data reported favorable results, especially with respect to thrombogenicity [30]. Experiments in dogs showed that gold produces less intimal proliferation than stainless steel [31]. Nevertheless, a recently published randomized study comparing gold-coated stents with uncoated ones in patients with coronary artery disease showed an increased risk of restenosis after placement of gold-coated stents [32]. The authors speculated that different techniques of gold coating might account for its unfavorable effect. This hypothesis is supported by the results of Edelman et al. [33] showing that the processing of gold coating fundamentally determines the degree of intimal proliferation in a porcine model.

Carbon Coating

In its pure form, carbon exists in two different crystallographic modifications, as diamond and graphite. Although experimental studies report that graphite enhances thrombogenicity [34], it is currently used as a surface coating for artificial heart valves [35]. It is known from experimental settings that metal ions evoke an inflammatory tissue response [36]. Therefore, attempts have been undertaken to use diamond-like carbon modifications as a barrier coating to reduce metal ion release. In-vitro experiments showed a marked reduction in platelet activation and thrombogenicity [37]. Another principle has been used in the manufacture of the Carbostent (Sorin Biomedica, Table 2). In this method the stent is coated with pure carbon characterized by a polycrystalline structure. Experimental studies suggest that biocompatibility is ameliorated [38], and preliminary clinical results report an angiographic restenosis rate of 11 % after implantation of the Carbostent [57].

Coating with Semiconductor Materials

It is well accepted that platelet activation and thrombus formation are critical steps in the development of restenosis. It has long been known that thrombus formation is based on electronic processes, and semiconductor layers for stent coating have been developed based on that knowledge. The prototype of this coating is a hypothrombogenic semiconducting ceramic coating made from amorphous hydrogenated silicon carbide (SiC). This material is able to suppress the electron transfer, which is crucial in the transformation of fibrinogen into fibrin. Experimental studies using SiC as a semiconductor stent coating showed a marked reduction in fibrin and thrombus deposits [39]. Based on this theoretical background, SiC-coated stents were used in patients with acute myocardial infarction with promising long-term results [40]. Especially in this clinical setting, where thrombosis plays a major role, the antithrombotic properties of this coating might be favorable.

			Clinical Studies	
Stent	**Coating**	**Company**	**Feasibility**	**Randomized Coated vs uncoated**
BiodivYsio	Phosphorylcholine	Biocompatibles Cardiovascular Farnham, UK	Galli et al. [57]	Not available
Carbostent	Ppyrolytic carbon	Sorin Biomedica Saluggia, Italy	Antoniucci et al. [58]	Not available
MAC-Carbon-Stent	Carbonisation (no details available)	amg Raesfeld-Erle, Germany	Voigt et al. [59]	Not available
Tensum III/TENAX	Silicon carbide	Biotronik Berlin, Germany	Heublein et al. [60]	Not available
NIRoyal	Gold	Boston Scientific SCIMED Maple Grove, U.S.A.	Cremonesi et al. [61]	Not available
INFLOW Stent	Gold	InFlow Dynamics AG München, Germany	Kastrati et al. [32]	Not available
Jomed Coronary Stent Graft	PTFE membrane	Jomed Helsingborg/Sweden	Baldus et al. [62]	Not available

Table 2. Commercially available coated stents.

Membrane Covered Stents

A totally different method has been chosen in covering the entire stent with a polymer membrane. Using this technique, a polytetrafluoroethylene (PTFE) membrane is mounted between two stents in order to diminish peri-interventional thrombus embolization. Although using this approach did not enhance the biocompatibility of the stent, the first clinical experiences looked promising [41]. Preliminary data suggest that this stent might be a superior treatment strategy in the special clinical setting of stenting of aortocoronary bypass grafts [61].

Drug Coating

Many drugs have been successfully tested to prevent restenosis in animal models but most were ineffective in clinical trials in humans [42-44]. Agents that were effective in animal models included angiotensin-converting-enzyme inhibitors [45], anticoagulants [46], calcium channel blockers [47], and antiplatelet drugs [48]. One reason for the divergent results in animal models and clinical studies might be that no sufficient local drug concentration in the coronary vessel wall of humans can be achieved through oral administration. These observations resulted in the concept that a much higher local concentration can be achieved by using stents as delivery systems for antiproliferative drugs. Driven by this idea, antiproliferative agents have been bound onto stent surfaces with promising results in the animal model (Table 1). However, recent results in small selected patient groups showed potential risks when antiproliferative drugs were delivered onto coronary stents. As these substances do not selectively inhibit smooth muscle cell proliferation, but instead prolong re-endothelialization of stent struts, the risk of subacute stent thrombosis might be higher. As in coronary brachytherapy, the interventional cardiologist is faced with new problems in applying new techniques of stent coating, and further studies will show whether the advantages outweigh the potential risks.

Conclusion

Although many attempts have been undertaken to increase the biocompatibility of coronary stents, finding the ideal stent material and stent design is still a challenge for modern cardiology. As stent coating offers the opportunity to combine mechanical properties and biocompatibility of different materials, this is a promising direction for future research. In addition biocompatibility can be increased and drugs applied in order to reduce intimal proliferation. Although promising results were achieved in animal models and preliminary clinical studies, large randomized studies will need to confirm the present findings before the chapter on restenosis in interventional cardiology can be closed.

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