Stent Coating or Brachytherapy? Their Future Role in Endovascular Therapy of Coronary Artery Disease

J. J. R. M. BONNIER
Catharina Hospital, Eindhoven, The Netherlands

Summary

The past few years have seen an increase in the use of stent coatings, due to a number of disadvantages associated with metallic stent surfaces. Several coatings of stainless steel stents were tested in vitro and in vivo to prove that they would lower the (sub)acute thrombosis rate and initial hyperplasia. In addition, brachytherapy — radiation of the stented area from the inside — has been used for several years with good results in treating in-stent restenosis. Both beta- and gamma-radiation have proven their effectiveness in this field. The presented article compares both therapy modalities and discusses their potential.

Key Words

Stent coating, brachytherapy, restenosis

Introduction

Continuous improvement in stent design, the application of different coatings, and the combined use of ticlopidine or clopidogrel with aspirin have reduced the incidence of acute coronary stent thrombosis to less than 2 % [1-3]. In long-term follow-up, restenosis percentages were reduced, depending on the definition used: re-coronary angiographic restenosis occurred in 15 % to 25 % of all cases; target vessel revascularization (TVR), in less than 10 %. In-stent restenosis due to neointimal hyperplasia following stent implantation is still a limitation in coronary interventions [4].

Intracoronary brachytherapy with beta- or gamma-radiation was developed to suppress excessive tissue response to the implanted prosthesis [5,6]. The use of stent coatings could theoretically achieve the same results by minimizing the reaction of the vessel wall to the implantation of metallic prostheses (stents) in coronary vessels. This article reviews the current knowledge concerning both methods and discusses the differences in application.

Restenosis

The Achilles heel of every coronary intervention is the restenosis process. For interventions with conventional balloon angioplasty, it occurs at a rate of 35 % to 50 %. With the use of stents, it diminishes to 25 % or less, depending upon the kind of stent or the restenosis definition used [7].

The total process after dilatation includes four phases:

- Early elastic recoil, occurring immediately after balloon dilatation.
- Mural thrombus formation in the first hours after the intervention.
- Neointimal proliferation, starting with the inflammation phase 2 to 4 days after the intervention when platelet-derived growth factor/tissue growth factor (PDGF/TGF) is released from alpha granules, resulting in smooth muscle cell modulation and proliferation. The endothelial cells migrate from the wounded edge.
- Chronic geometric changes, with a permanent remodeling of the vessel.

The incidence for the occurrence of restenosis is shown in Table 1.

Nowadays, we have different options to counter the individual phases. In dealing with early elastic recoil, we want to achieve a greater minimal lumen diameter (MLD). This is achieved by implanting a stent. To avoid mural thrombus formation, several agents are

Time	Occurence of restenosis
Day 1	10 % to 15 %
Month 1	15 %
Month 1 to 3	35 % to 45 %
Month 3 to 6	rare
Month 6 to 12	rare

Table 1. Incidence for the occurrence of restenosis.

available, such as IIB/IIIA antagonists and other agents inhibiting thrombus formation and platelet aggregation. In the future, molecular therapy may play a role. Neointimal proliferation can be suppressed by radiation, anti-proliferative agents, and molecular therapy. Chronic geometric changes can be prevented by implanting stents in order to achieve the greatest MLD. For the lowest restenosis rate possible, a combination of the various methods can be used:

- stent
- drug delivery
- brachytherapy

} or combination

Interactions between Stent, Blood, and Vascular Tissue

The stent material mainly interacts with blood and vascular tissue [8]. A thrombotic response is caused by the surface characteristics of the stent. The mechanical properties of the stent influence wound healing after implantation [9].

Stainless steel is the most frequently used stent material due to its favorable mechanical properties. However, it is known to induce platelet adhesion and can be potentially thrombogenic in blood. By releasing small amounts of heavy metal ions, it can interact with blood and tissue cells, a process that plays a role in starting the inflammatory phase [10].

To minimize all these potential disasters, other stent materials have been tested, such as tantalum and nitinol. However, this did not result in a better long-term clinical performance. Different coatings were therefore developed to modify the outer stent surface for better biocompatibility. The ideal coating should be hemocompatible to prevent (sub)acute stent thrombosis, and it should have an improved tissue compatibility, to reduce neointimal proliferation and, thus, restenosis.

Stent Coatings

There are several kinds of coatings available.

- Heparin-coated stents [11,12]. Coating stainless steel coronary stents with heparin should inhibit the activation of the coagulation process, increase the inhibition of activated coagulation enzymes, inhibit platelet aggregation, and reduce late intimal hyperplasia. However, the Benestent II pilot study [13] and the Benestent II randomized trial [14] did not show any differences compared with uncoated stents in regard to long-term clinical outcome. The subacute stent thrombosis rate was very low, but it was not proven that this was due to the coating.
- Gold-coated stents. Gold is widely used in medical products, but there are also reports that it is inferior when compared to uncoated stainless steel stents. The material does not corrode, and it is chemically inert and highly biocompatible [15]. However, other investigations showed a thrombogenic behavior [16] and disappointing clinical results [17] of gold-coated stents. The NIRoyal (Scimed, USA) is an example of such a stent. The NUGGET trial should answer the question whether there is a difference between stainless steel stents with and without gold coating.
- Stents coated with turbostratic carbon. This principle is utilized in the Carbo stent (Sorin, Italy). Here, a modified plasma gas discharge deposition at low temperatures is used to achieve a 0.3 to 0.5 μm carbo-film coating on previously mirror-polished stainless steel coronary stents. In animals, a minimal degree of thrombus deposition and a mild neointimal proliferation could be reported [18]. The preliminary clinical results were very good with a TVR of 8 %.
- Phosphorylcholine-coated stents. This coating consists of a synthetic polymer and provides very good biomimicry. It has shown excellent blood and tissue compatibility with no adverse tissue reaction in animal studies [19]. In humans, good results were obtained in small vessels, making this a promising approach.
- Silicon carbide coated stents. The transformation of fibrinogen to fibrin involves an electron transfer from the fibrinogen molecule to the solid surface of a stent. Thus, the electronic structure of both the fibrinogen molecule and the stent surface determine the thrombogenicity [20]. These observations led to the

idea to block the transformation of fibrinogen to fibrin with a silicon-carbide coating. The Tenax coronary stent (Biotronik, Germany) has such a coating. Several clinical studies involving the Tenax stent have shown a low TVR and a high rate of event-free survival [21]. There are several ongoing studies, such as TRUST, to prove the concept.

Brachytherapy

Brachytherapy is a radiation therapy modality that places radioactive sources ("seeds" or wires) in or near the tissue to be radiated. The radiation is emitted outward, unlike conventional external beam radiotherapy, where radiation must traverse normal tissue in order to reach its target. The word "brachytherapy" means "short therapy", which implies that the radiation is limited to short distances.

The use of radiation to treat restenosis is still experimental, but several studies are under way to prove the concept. During brachytherapy, radiation appears to reduce intimal proliferation caused by increased tissue growth rates. It seems to have a positive impact on vessel remodeling or contraction, and it allows vessel healing to continue. It should work, because it has been used for more than 50 years in treating proliferative cell disorders, such as cancer and keloids.

Radiation selectively targets rapidly dividing cells. To prove that it is really an effective cure for (in-stent) restenosis, radiation therapy is now being investigated in several randomized studies: the beta-cath, which applies beta radiation, and also several gamma radiation trials (SCRIPPS, WRIST, GAMMA I, LONG-WRIST).

Brachytherapy is still in its infancy, and several questions remain unanswered (e.g., What is better, beta or gamma radiation?) It can also lead to some new complications, such as late thrombosis or geographical mismatch ("candy wrapper", "lollypop"). Radioactive stents have not yet been proven to be better than conventional stents. Therefore, they are not useful to date.

Conclusion

The whole issue concerning the use of stents with coatings or brachytherapy is still unclear. Currently, it cannot be answered which of the two methods is better.

Coatings on stents are attempting to interrupt the restenosis process in another phase, rather than using radiation. To date, radioactive stents with proven efficacy do not exist. Therefore, it is too early to say whether stents with coatings or radiation are better. Maybe the future will show that they are complementary. Theoretically, coated stents have the advantage of inhibiting coagulation and platelet aggregation and reducing proliferation and restenosis. Radiation should lead to less restenosis by minimizing proliferation. Both therapeutic approaches must be proven in prospective randomized trials [22].

References

[1] Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anti-coagulation accomplished with intravascular ultrasound guidance. Circulation. 1995; 91: 1676-1688.

[2] Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet therapy after the placement of coronary artery stents. N Engl J Med. 1996; 334: 1084-1089.

[3] Moussa J, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation. 1999; 99: 2364-2366.

[4] Haase J, Geimer M, Göhring S, et al. Results of micro-stent implantations in coronary lesions of various complexity. Am J Cardiol. 1997; 80: 11-12.

[5] Teirstein PS, Massullo V, Jani S, et al. Catheter based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med. 1997; 336: 1697-1703.

[6] Waksman R, White RL, Chan RC, et al. Localized intracoronary radiation therapy for patients with in-stent restenosis: preliminary results from a randomized clinical study. Circulation. 1997; 96: I-219.

[7] Haudenschild C. In: Textbook of Interventional Cardiology. Chapter 20. Topol E (ed.). W. Saunders, Philadelphia, 1994.

[8] Spector M, Caese C, Tong LiX. The local tissue response to biomaterials. Crit Rev Bio. 1989; 5: 269-295.

[9] Baier RE. Selected methods of investigation for blood-contact surfaces. In: Blood in Contact with Natural and Artificial Surfaces. Leonhard EF, Turitto VT, Vroman L (eds.). NY Academy of Sciences, New York, 1987: 68-77.

[10] Tracana RB, Sousa JP, Carvallo GS. Mouse inflammatory response to stainless steel corrosion products. J Mater Sci. 1994; 5: 596-600.

[11] Larm O, Larsson R, Olsson P. A new non-thrombogenic surface prepared by selective covalent binding of heparin via a modified reducing terminal residue. Biomat Med Dev Artif Organs. 1983; 11: 161-163.

[12] Hoffman J, Larm O, Scholander E. A new method for covalent coupling of heparin and other glycosaminoglycans to substances containing primary amino groups. Carbohydr Res. 1983; 117: 328-331.

[13] Serruys PW, Emanuelsson H, Giessen WJ van der, et al. Heparin-coated Palmaz-Schatz stents in human coronary arteries: early outcome of the Benestent-II Pilot study. Circulation. 1996; 93: 412-422.

[14] Serruys PW, Hout B van, Bonnier H, et al. Randomized comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (BENESTENT-II). Lancet. 1998; 352: 673-681.

[15] Beythien C, Gutensohl K, Kühnl P, et al. Influence of "diatometry" analysis in a pulsed floating model. J Am Coll Cardiol. 1998; 31: 413A.

[16] Sawyer P.N, Brattain W.H, Boddy P.J. In: Biophysical mechanism in vascular hemostasis and intravascular thrombosis. Sawyer PN (ed.). New York: Appleton-Century-Crofts, 1965: 337-348.

[17] Schömig A, Kastrati A, Dirschinger J, et al. Randomized comparison of gold-plated steel stent with conventional steel stent: Results of the angiographic follow-up. JACC. ACCIS'99; 1217-54 (abstr.).

[18] Virmani R, Santarelli A, Galloni M, et al. Tissue response and biocompatibility of the Sorin CarboStent: experimental results in porcine coronary arteries. Am J Cardiol. 1998; 82 (Suppl. 7A): 658 (abstract).

[19] Whelan DM, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart. 2000; 83: 338-345.

[20] Rzany A, Schaldach M. Physical properties of antithrombogenic materials - an electronic model of contact activation. Prog Biomed Res. 1999; 1(4): 59-70.

[21] Hanekamp CE, Bonnier H, Michels RH, et al. Low target vessel revascularization after intracoronary silicon carbide coated stent implantation. Prog Biomed Res. 1999; 1(4): 96-98.

[22] Haase J. Stent coatings: how to reduce the biological response to vessel wall imaging. J Interven Cardiol. 1999; 12: 439-444.