

Prevention of Restenosis after Percutaneous Coronary Intervention: The Continuing Challenge

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Abstract

Percutaneous coronary intervention with angioplasty and stenting is well established in the treatment of coronary artery disease. However, the many advances in technique and equipment over the last couple of decades have yet to significantly reduce the incidence of restenosis. This Achilles' heel has necessitated frequent re-interventions and also introduced a new iatrogenic disease of in-stent restenosis. Brachytherapy and coated stents may be the answer to this difficult problem. Many papers have been published in the last few years on these two new modalities of treatment, and we review the evidence available so far. Early results show that brachytherapy significantly reduce the incidence of restenosis when used in restenotic lesions, and coated stents significantly reduce restenosis in de novo lesions. This early promise of brachytherapy and coated stents, if confirmed in longer-term studies, will represent a breakthrough in the battle against restenosis and may dramatically change the practice of interventional cardiology in the near future.

Ann Acad Med Singapore 2002; 31:102-6

Key words: Angioplasty, Brachytherapy, Restenosis, Stent

Introduction

Since Andreas Gruntzig first demonstrated its use in humans in 1977, the utilisation of percutaneous transluminal coronary angioplasty (PTCA) has grown tremendously throughout the world today. The ability to treat coronary artery stenosis with this minimally invasive alternative to coronary artery bypass surgery is attractive to both cardiologists and patients alike. However, despite many advances in the field of interventional cardiology, the Achilles' heel of angioplasty remains the problem of restenosis, which occurs in 30% to 50% of patients going for PTCA, usually within the first 6 months.¹ This necessitates repeat angioplasty procedures with additional costs and patient risks. It has also introduced a new iatrogenic entity of in-stent restenosis.

The mechanism of restenosis is complex, but there are essentially two components. Firstly, there is the mechanical component of elastic recoil and geometric remodelling of the vessel after being stretched. Secondly, there is the biological response consisting of smooth muscle cell proliferation with neointimal proliferation and hyperplasia. Both of these are part of the complex vascular 'healing' response to the mechanical trauma caused during PTCA.

Coronary stent provides mechanical scaffolding that

virtually eliminates the recoil and remodelling components of restenosis, and is the only device in regular use proven to reduce the incidence of restenosis after PTCA. In the STRESS Trial, patients with *de novo* lesions, randomised to stent implantation, had a 31.6% rate of restenosis compared to 42.1% in the balloon angioplasty group ($P < 0.05$).² In the BENESTENT Trial, patients with *de novo* native lesions, randomised to stent implantation, had a 22% rate of restenosis compared to 32% in the PTCA group ($P = 0.02$).³

Stenting, however, worsens the proliferative response, but the larger luminal diameter produced by stenting reduces the significance of the restenotic response in the majority of cases. However, it has become obvious that no current mechanical intervention can successfully eliminate restenosis by itself unless the underlying intimal hyperplastic response can be controlled. Currently, the two most promising approaches available to tackle this problem are brachytherapy and the use of drug-eluting stents.

Brachytherapy

Radiation therapy has been used to treat benign disorders, such as keloid scars, as well as malignant diseases, for over 100 years. The use of radiation to prevent restenosis, by

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attenuating the hyperproliferative response after coronary intervention, has been investigated extensively for the best part of the last decade. Experience with external beam radiation (EBR) was disappointing, with evidence of accelerated neointimal proliferation in animal studies.⁴ The problem may lie with the fact that in EBR, the dose of radiation is delivered homogeneously to a large volume of tissue around the affected coronary vessel. Intraluminal brachytherapy is now the preferred method, which allows a more site-specific delivery of a radiation dose from within the coronary artery, with doses delivered preferentially to the intima.

There are basically two types of radiation sources, which emit either gamma or beta-radiation. Gamma-emitters are high energy, with the disadvantage of requiring complex shielding in the cardiac lab when it is being used. Beta-emitters are of lower energy, with dramatic attenuation of energy over a very short distance and minimal penetration beyond the coronary artery. This brings the considerable advantage of ease of use, with much lesser shielding requirements, as well as minimising the ionising exposure to both the operator and the patient.

The radiation can be delivered by various devices. The Novoste Beta-Cath system uses a train of small cylindrical sealed sources ('seeds') containing strontium-90, which is delivered into a multi-lumen delivery catheter positioned over a guide-wire. A recent study utilised an angioplasty balloon filled with ¹⁸⁸Re, which is a beta-emitter in liquid form.⁵ We recently participated in a brachytherapy trial (BETTER) which used a novel system where the beta-emitting ³²P radioisotope was placed within the balloon membrane of an angioplasty-like catheter. Radioactive stents are also available but its efficacy has been disappointing so far. The National Heart Centre utilises the Guidant Galileo intravascular radiotherapy system which uses a ³²P-source wire positioned with a centering catheter (Fig. 1). Our preliminary experience has been encouraging especially in the treatment of in-stent restenosis.

In the SCRIPPS Trial, 55 patients with previous restenosis after angioplasty were recruited in a double-blind, randomised trial comparing Iridium-192 (¹⁹²Ir), a gamma-emitter, with placebo. In the ¹⁹²Ir-treated group, target-vessel revascularisation was significantly reduced by 74% at 6 months and 68% at 3 years. Angiographic restenosis was reduced by 69% at 6 months and 48% at 3 years. No adverse effects related to brachytherapy were noted.^{6,7} In the Gamma-One trial, intracoronary irradiation with ¹⁹²Ir showed promise as an effective therapy for the specific problem of in-stent restenosis.⁸ The BERT trial involving 23 patients with *de novo* lesions found the use of endovascular beta-radiation (⁹⁰Sr/Y sources) after balloon angioplasty to be safe with a lower-than-expected rate of

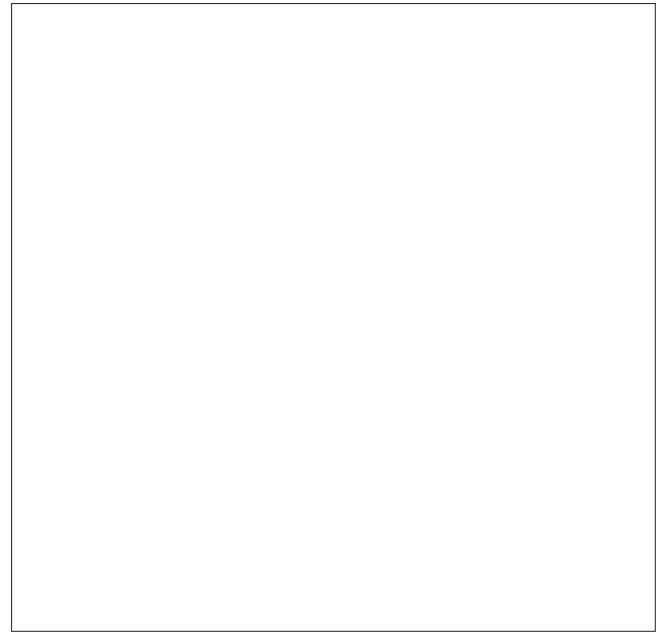


Fig. 1. This patient had an in-stent restenosis in the proximal left anterior descending artery (A, arrow). Balloon angioplasty was performed with good procedural outcome (B), and brachytherapy with the Guidant Galileo system was then applied (C; arrows indicate the radiation zone). The 6-month follow-up angiography showed that the previously stenotic area remained widely patent (D).

restenosis of 15% at 6 months. There was also significantly reduced treatment time and operator exposure compared with previous trials using the gamma-emitter ¹⁹²Ir.⁹ PREVENT, a randomised, sham-controlled trial involving 105 patients with restenotic or *de novo* lesions, showed that intracoronary brachytherapy with the beta-emitting ³²P source wire is safe and highly effective in inhibiting restenosis at the target site at 6 months (8% versus 39%; $P = 0.012$).¹⁰ A recently published trial also showed that intracoronary beta-radiation therapy produces a significant dose-dependent reduction in the rate of restenosis at 6 months after successful balloon angioplasty of a previously untreated coronary stenosis.¹¹

It must be noted that most of the brachytherapy trials that demonstrated benefit predominantly involve patients with previous coronary angioplasty or in those with in-stent restenosis. The current evidence is less promising with regards to the use of brachytherapy in *de novo* lesions. In the recently presented Beta-Cath System trial, which evaluated the use of beta radiation in treating *de novo* or unstented lesions in 1455 patients, there was no significant reduction in clinical restenosis at 8 months. This was due to the fact that although brachytherapy has reduced angiographic restenosis within the radiated segment, it also increased restenosis at the lesion edges ('edge effect'). Further refinement in brachytherapy techniques may well solve this problem in the near future. In the meantime, the Food and Drug Administration (FDA)

in America currently only approves of the use of brachytherapy in the treatment of in-stent restenosis.¹²

Despite the overall encouraging results shown so far, there has been some reluctance to whole-heartedly embrace this promising but expensive new technology at this point in time. A few complications specifically associated with brachytherapy have been identified. Firstly, there is the threat of late thrombosis, which is defined as any angiographically documented total occlusion >30 days after the procedure. The occurrence of this may be related to ionising radiation causing delayed re-endothelialisation, fibrin deposition and platelet recruitment, tissue erosion around the stent, impaired vasoreactivity or spasm, or unhealed dissection. This complication varies between 6.6% and 10% in small reported series but it is hoped that these figures may be reduced with a more prolonged anti-platelet regimen with aspirin and ticlopidine or clopidogrel. Late thrombosis rates also appear to be higher when stents are used. In the SCRIPPS trial, patients were given aspirin and ticlopidine for 3 months if new stents were implanted. However, the most effective anti-platelet regimen has yet to be determined.¹³ Another limitation is the potential to cause 'edge effect' or 'candy wrapper' lesion, so called because of the significant renarrowing at the stent edges that occur together with the absence of restenosis in the main part of the stent, leading to a unique form of intralumen stenosis. This phenomenon is thought to be due to 'geographic miss', a term used to describe an arterial segment subjected to the barotrauma of balloon angioplasty or stenting, but receiving sub-optimal doses of radiation.¹⁴ The incidence of this complication may be reduced by not oversizing the angioplasty balloon, as well as careful matching of the area of irradiation to the area of artery injured by intervention. There is also some concern that the inhibition of healing response or excessive radiation dosage may lead to coronary aneurysm formation, although this was not observed in the SCRIPPS trial at 3 years follow-up.⁸ The two questions on most cardiologists' mind, unfortunately, cannot be answered at the present moment in the absence of long-term data. Is brachytherapy preventing the restenosis process or simply delaying it? What is the likelihood of developing malignancy in the future, even with the use of such low dose radiation? The answers will be clearer in the years to come.

Coated Stents

Another novel idea in trying to prevent restenosis is to coat the usual stainless steel coronary stents with another material. Coated stents can be simply divided into two types: those with a passive coating and those with a biologically active coating.

Surface Modified Stent (Passive Coating)

Different types of coating on stent can be used to provide a biologically inert barrier between the stent surface and the blood circulation. Commercially available coated stents include the gold-coated Inflow and NIR Royale stents, the silicon-carbide-coated Tensum and Tenax stents, and the diamond-like carbon-coated Diamond AS and Diamond Flex stents. The rationale is that these devices may improve biocompatibility by preventing the activation of blood components, and also reduce stent corrosion after deployment that could provoke inflammatory process of the coronary wall tissue.

In vitro, gold-coated stents had been shown to reduce platelet activation and thrombus mass, as well as a thinner neointima formation compared with stents plated with other metals. Another property of the gold-coated stent is its radio-opacity and this is useful in treating lesions where precise placement of the stent is required, such as ostial and bifurcational lesions. However, a randomised study comparing gold-coated Inflow stent with uncoated Inflow stainless steel stent in 731 patients suggested an increased risk of restenosis and clinical events.¹⁵ This may be due to the poor manufacturing process of the gold coating for that particular stent, resulting in a rough surface encouraging neointimal proliferation. Results from the NIR Royale gold-coated stent registry showed similar restenosis rate and major adverse cardiac events (MACE) at 6 months compared to other published trials using stainless steel stent.¹⁶ Currently, we are participating in a large multi-centre trial (NUGGET) comparing the NIR Primo stent (stainless steel) to NIR Royale stent (Gold) in *de novo* coronary artery lesions. Over six hundred patients have been enrolled worldwide, and the 6 months clinical and angiographic results would be available later this year. This may help to resolve the controversy of gold coating.

Surface Modified Stent (Biologically Active)

Pharmacological therapy of restenosis has not been very successful, probably because the agents given systematically cannot reach sufficient concentrations in the coronary arteries to significantly impact on the restenotic process. Thus, local delivery of a drug in the form of a stent coating might be able to achieve significantly higher tissue levels than could be achieved with systematic administration. Biologically active coated stents, such as the heparin-coated stents or phosphorylcholine-coated stents, have already been shown to reduce the rate of subacute thrombosis. Theoretically, these stents may reduce the current necessity for aggressive post-stenting antiplatelet regimen with drugs such as ticlopidine or clopidogrel.^{17,18}

While the above stent coatings are designed primarily to reduce the rate of thrombosis, newer agents that influence



Fig. 2. Diagrammatic representation of the cell proliferation cycle. This consists of a mitosis phase (M), followed by a gap phase (G_1), a period of nuclear synthesis (S) and another gap phase (G_2) before mitosis occurs again. After mitosis, certain cells remain quiescent (G_0). Paclitaxel inhibit cell replication predominantly in the G_1/G_2 and G_2/M phases, while sirolimus induces cell-cycle arrest early in the late- G_1 phase.

the actual neointimal hyperplastic process are now being evaluated. One such promising drug is paclitaxel (Taxol), the first representative of a new class of microtubule-affecting drugs that exerts a very potent, dose-dependent inhibitory effects on smooth muscle cells proliferation and migration (Fig. 2). It is an anti-neoplastic agent which has been used in the treatment of various tumours, such as small cell lung cancer, ovarian and breast carcinoma. Unlike other anti-proliferative agents, paclitaxel also has several properties that make it a good candidate for local drug therapy in restenosis after balloon angioplasty or stent implantation. First, the highly lipophilic character of paclitaxel promotes a rapid cellular uptake by enabling it to easily pass through the hydrophobic barrier of cell membranes. Second, the unique mode of action supports a long-lasting anti-proliferative action even after a brief, single-dose application at very low concentrations, as previously shown in tumours cells.^{19,20} The early trials using paclitaxel-eluting stents have shown significant inhibition of restenosis. One recent study involving 26 patients with *de novo* lesions compared the use of paclitaxel-eluting with ordinary stent. At 18 months follow-up, the restenosis and MACE rate was 0% for the drug-eluting stent, compared to 54% and 15%, respectively, for the ordinary stent. There was no significant clinical side effect. A randomised European multi-centre trial is ongoing, enrolling a total of 300 patients.²¹

The other promising anti-proliferative drug is sirolimus (Rapamycin), a natural macrocyclic lactone, which is a potent immunosuppressive agent used for prophylaxis of renal transplant rejection. It has been shown *in vitro* to inhibit smooth muscle cells proliferation and reduce intimal thickening in models of vascular injury. Its pharmacokinetic properties, such as the lipophilic characteristic, make it an

ideal candidate to be used for stent-based delivery. A pilot study with the sirolimus-coated BX velocity stent performed in 30 patients with *de novo* native coronary artery showed promising results. There was no incidence of restenosis at 4 months follow-up and no MACE was seen at 8 months.²² The one-year angiographic follow-up recently presented confirms that the minimal amount of neointimal hyperplasia seen at 4 months is again observed at 1 year, together with no MACE.²³

Conclusions

Brachytherapy and coated stents are currently the two most promising interventional approaches to solve this vexing problem of restenosis. With the current available evidence, brachytherapy remains the established treatment modality in terms of number of patients and longer follow-up. However, the brachytherapy trials so far suggest that its benefit is in patients who has had previous coronary intervention or in those with in-stent restenosis. On the other hand, the early trials of drug-eluting stents that show significant reduction of restenosis involve mainly *de novo* lesions. In the longer term, drug-eluting stents may hold the most potential, as they are much simpler to use in comparison to brachytherapy, and also do not require any new expertise or additional equipment. Clearly, further refinement of techniques, as well as further trials are required for both modalities. If either treatment modality can truly reduce the spectre of restenosis significantly, then this could be the next major revolution in the practice of interventional cardiology as well as the treatment of coronary disease altogether.

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