Radioactive stents to reduce restenosis: time for an epitaph?

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Stents are playing an increasingly important role in percutaneous coronary interventions and they seem to be here to stay. They are easy to implant, safe with new antiplatelet agents and have been shown to reduce restenosis, by eliminating local recoil of the vessel wall, mainly in large vessels and in discrete lesions. However, they have created the new problem of in-stent stenosis, exclusively due to neointimal hyperplasia, and some concern still exists regarding the late arterial wall response, as potentially favourable positive remodelling is also prevented by stents.

The dream of all interventional cardiologists is, one day, to have stents without restenosis. During more than 20 years, the pathobiology of restenosis has stimulated, continuously and extensively, basic and clinical research. Much is already known but the process is, unfortunately, very complex, with too many players involved with iatrogenic aggression to the atherosclerotic plaque and the different components of the arterial wall. To complicate the issue, restenosis varies from place to place, within the same coronary artery or the same patient, and in spite of the same degree of aggression, for instance, the same stent delivery pressure.

The battle against restenosis, particularly in-stent restenosis, continues and is the focus of all our attention. Stimulated by researchers, this battle is also a formidable challenge to the industry, forced to respond to the needs of clinicians and to save the ‘golden egg’ represented by stents.

Ionizing radiation has emerged in the last few years as a potentially important way of reducing restenosis. It provides non-specific breaks in chromosomal DNA and is an effective and potent antiproliferative, when cells are actively dividing at the time of exposure. The concept is simple and radiation therapy appears to be ideally suited for in-stent restenosis

Catheter-based intravascular brachytherapy, mainly from gamma and beta sources, based on results in animal models of restenosis demonstrating inhibition of smooth muscle cell proliferation and neointimal hyperplasia, is being clinically used. After careful dose-response studies, which engaged a multidisciplinary clinical research team including radiation oncologists and physicists, results of recent multicentre randomized trials have shown its safety and efficacy. Some drawbacks have already been revealed, however, such as late vessel thrombosis requiring more aggressive and extended antiplatelet therapy and the so-called ‘geographic miss’, producing edge stenosis due to inadequate radiation.

Within the context of vascular radiation, the idea of a radioactive stent is, indeed, attractive. Stents would now be used as a platform for local radiation delivery, and they would control the intimal hyperplastic response. In opposition to catheter-based methods, radioactive stents would be simpler, quicker and safer, because of lower radiation activity and lack of dosimetry constraints.
Radioactive stents were patented in the U.S.A. in 1991. In-vitro studies were started in 1992 and the first clinical application was performed in 1996\(^5\). This was a very carefully planned and complex learning curve, based on a variety of experimental dose-response studies in different species, on knowledge of variables that might possibly affect dosing to the target tissue, on time of peak of action and depth of radiation, etc. In spite of the difficulties in extrapolating in-vitro dose-response data to humans, stent radiation used clinically has been up to \(24 \cdot 0 \mu \text{Ci}\) radioactivity of \(^{32}\text{P}\).

Only a few highly selected centres have so far been involved in clinical research on the feasibility and safety of radioactive stents. This research has almost exclusively used stents prepared by direct ion implantation of \(32\)-phosphorus, which is a pure \(\beta\)-particle emitter (\(^{32}\text{P}\) stents).

In the 1A phase of the Isostents for Restenosis Intervention Study (IRIS)\(^6\) very low activity (0.5–1.0 \(\mu \text{Ci}\)) \(^{32}\text{P}\), 15 mm-long Palmaz–Schatz coronary stents (32 patients) were used and in phase 1B\(^7\) (multicentre) the stent activity was increased to 0.75–1.5 \(\mu \text{Ci}\) (25 patients). The patients had de novo or restenosis native coronary lesions, there were no major cardiac adverse events or stent thrombosis, but the restenosis rate was not different from that expected with conventional stents, meaning that with these low activity stents, the neointimal responses were not significantly altered.

The single centre non-randomized Milan Dose-Response Study, recently reported\(^8\), used \(^{32}\text{P}\) stents (Palmaz–Schatz or BX Isostent) and various activity levels: group 1, 0.75–3.0 \(\mu \text{Ci}\); group 2, 3.0–6.0 \(\mu \text{Ci}\); group 3, 6.0–12.0 \(\mu \text{Ci}\), in 82 patients (122 stents of 15 mm to cover lesion lengths up to 28 mm). The study confirmed the feasibility of the \(^{32}\text{P}\) radioactive \(\beta\)-emitting stents (only one stent thrombosis) and a 6-month dose-related reduction of in-stent neointimal hyperplasia (16%, 3% and 0%, for the three groups, respectively). However, the intra-lesion restenosis was high (52%, 41% and 50%, for the three groups, respectively) due to stenosis at the edges of stents, what the authors have called the ‘candy wrapper’ effect.

In 1999 the Rotterdam group first reported\(^9\), their contribution to the IRIS study using the \(^{32}\text{P}\) stent with a radioactivity of 0.75–1.5 \(\mu \text{Ci}\) in 26 patients (31 stents). They confirmed the safety and feasibility of the radioactive stent with no major cardiac adverse events at 6 months, including no subacute thrombosis, an in-stent restenosis of 17% (88% angiographic follow-up) and no restenosis at the stent edges.

In the current issue, Wardeh et al.\(^{10}\) report the latest Isostent Thoraxcenter experience with a radioactivity of 6–12 \(\mu \text{Ci}\), as part of a multicentre European dose response trial evaluating the \(^{32}\text{P}\) radioactive stent. With 42 BX Isostent stents implanted in 40 patients, in discrete lesions (only two patients required two stents) and reasonable size vessels, there were two total occlusions and 44% stent edge restenosis (90% angiographic follow-up). Interestingly, both total occlusions and 71% of the edge restenosis occurred at the proximal edge of the stent. The study confirms the feasibility and safety of the \(^{32}\text{P}\) stent, as there was no restenosis within the stent, no major cardiac adverse events, only one early non-Q wave myocardial infarction and only 10 (25%) target lesion revascularizations.

The Milan group further pursued the previous study, with activities of 12.0–21.0 \(\mu \text{Ci}\) and a different approach to stent implantation, but intra-lesion restenosis remained high (30%)\(^{11}\). Results from the Vienna \(^{32}\text{P}\) dose response study\(^{12}\), with BX stents and initial activity of up to 24 \(\mu \text{Ci}\), confirmed, once again, the higher rate of edge restenosis. In their 36 patients this was responsible for 88% of the new revascularization procedures.

It is clear from all studies that radioactive stents can, in a dose response manner, almost abolish in-stent restenosis, but at the very high cost of creating a new, even greater, and so far unsolved problem of stent edge restenosis. The simple explanation for this phenomenon is geographic miss, lower radiation and balloon-induced trauma, all leading to intimal hyperplasia and negative remodelling. The subject has been extensively reviewed in an excellent editorial by Serruys and Kay\(^{13}\), where several theoretical suggestions urge more research and request new radioactive stent designs.

However, after several years of research it seems unlikely that radioactive stents will ever be launched into a big multicentre clinical trial or will become a clinically useful tool. The final and most important message of the paper by Wardeh et al.\(^{10}\) is quite clear and strong: ‘the radioactive stents are safe and feasible but, at present, they should not be clinically used’. With today’s knowledge, it seems that their epitaph has been written.

But new hopes are looming on the horizon of interventional cardiologists. For those who are stent oriented, drug-eluting stents such as rapamycin or paclitaxel, a polymer-coated stent, are already, or will soon be in clinical trials, and the first report, on a high-molecular-mass poly-L-lactic acid biodegradable stent in humans, has already been published\(^{14}\). Time will be the best judge of their future and only God knows how long we will have to wait for stents without restenosis.

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The heart failure epidemic: exactly how big is it?

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Introduction

Until recently, heart failure has been a much neglected condition and, to some extent, this is still true. There are many reasons why heart failure might be neglected. Probably one of the most important reasons has been the lack of good epidemiological data until now. Historically, this reflects the lack of practical definitions, the lack of simple diagnostic techniques and a lack of interest due to the lack of effective treatment\cite{1,2}. Guidelines, technological developments and pharmacological interventions have dealt with many of these deficiencies over the last 10 years\cite{1,2} and now we have the first glimmer of evidence that the prognosis of heart failure in the community is improving\cite{3}. Several comprehensive reviews of the epidemiology of heart failure and/or left ventricular dysfunction have been reported\cite{4,5,6,7,8,9,10,11}. However, relative to many other common cardiovascular diseases, the epidemiological science of heart failure is still in its infancy. Considerable thought is required to interpret the meaning behind the figures supplied so far.

Hedberg et al.\cite{6} (this issue) report a detailed cross-sectional survey of the population aged 75 years living in a Swedish town. Patients not only underwent interview but also ECG, exercise testing and echocardiography. This revealed that 6.8% had left ventricular systolic dysfunction, 6.7% had clinical heart failure, 9.9% had one or the other and 3.6% had both (Table 1). The authors point out that each of these figures is probably an under-estimate because some patients died between sampling and interview and a substantial number with or without known cardiovascular disease did not attend. This translates to about 100 people with heart failure or systolic dysfunction just aged 75 years in just one Swedish city (population 125 000).

The current report raises the issue of whether we should be screening for heart failure and ventricular dysfunction\cite{12}. If heart failure was a cancer, rather than just malignant, there is little doubt that population screening would have been adopted long ago. A detection rate of 10% is orders of magnitude better than most screening programmes for cancerous malignant...