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Editorials

The radioactive stent — any chance of a resurrection?

See page 1311 for the article to which this Editorial refers

Stent-based coronary brachytherapy to prevent restenosis has been studied in pre-clinical and clinical trials for almost a decade. In 1992, the first radioactive vascular prosthesis with which in vivo studies began was produced, by bombarding metallic stents with charged particles transforming some of the elements of stainless steel into radioisotopes[1–3]. Between 1992–1995, studies began to evaluate the scientific concept of radioactive stents. A 'proof of principle' was found, and techniques were developed to ease mass production[4,5]. After selective ion implantation of β-particle emitting radioisotopes into the surface of coronary stents was proven to be technically possible and cost-effective, and after early experimental results looked promising, enthusiasm over this new approach was generated worldwide.

Large scale clinical studies quickly originated in the U.S., stimulated by the growing clinical evidence that coronary stents were valuable instruments in interventional cardiology, despite the problem of in-stent restenosis, a problem still without a satisfactory solution. From June 1997 to 2000, several European Cardiology centres enrolled patients in dose-finding pilot trials with radioactive stents. These were set up to answer safety concerns, and to prepare for randomized, placebo-controlled multicentre studies. The first stent platform for an investigational, radioactive device, which was to be permanently implanted into patients, was a Palmaz–Schatz stent mounted onto a Cordis balloon expandable stent delivery system for the clinical trial IRIS (**I**sostents for **R**estenosis **I**ntervention **S**tudy)[6]. Restenosis at the articulation (bridge) of Palmaz–Schatz stents was discovered at the University of Heidelberg in 6 of 11 patients, and the stent design was changed to a BX stent platform without an articulation[6–9].

After enrolment of the first 100 patients in Europe, who were receiving β-particle emitting stents (isotope P-32) at activity levels between 1·5 and 12 μCi, it became clear that the benefit of inhibiting in-stent restenosis via stent-based beta-radiation was lost because of a new problem which interventional cardiologists called the 'edge-effect' or the 'candy-wrapper'. The edge-effect occurs at or beyond the stent margins and is defined as restenosis located outside the zone of therapeutic vessel irradiation.

In this issue, Kay *et al.* present a novel radioactive stent concept for the prevention of edge-effects[9]. The purpose of this elegant study was to determine whether a 'cold-end' of a radioactive stent prevents negative remodelling in the dose fall-off zone at or beyond the margins of the 'hot-stent' segment by scaffolding the vessel lumen. In Fig. 3 of their article, the authors present a schematic of lumen narrowing which occurred with their device. The authors demostrate that stent-based vessel irradiation prevents neointimal hyperplasia within the segment of the coronary artery that is irradiated but not within the non-irradiated segment[9]. It is interesting to note that the biological response to this mixed 'hot and cold' stent literally moved the edge-effect from the stent margin to the inside of the stent. Figure 3 shows that neointimal cells are piling up outside the radiation zone, and it is possible that inhibition of cell proliferation, by the segment providing vessel irradiation, is accompanied by inhibition of cell migration into the stent. This important observation came, at least in part, as a surprise.

Smooth muscle migration and proliferation are the major components of vessel wall reactions after stent implantation, and these processes are triggered by vascular injury[10]. Restenosis within stents is exclusively due to neointimal hyperplasia, and can only be completely prevented with a strong inhibitor of cell growth, such as ionizing radiation or a potent pharmacological agent[11]. Induction of clonogenic cell death and apoptosis are other mechanisms by which low dose rates of stent-based vessel irradiation may inhibit neointimal hyperplasia[12]. Every clinical study conducted so far uniformly concluded that radioactive stents are capable of reducing or even eliminating neointimal hyperplasia *within* the body of the stent. Beta-particle emitters in contact with the arterial wall are sufficient to induce cell death of the superficial smooth muscle cell layers, and are potent enough to inhibit proliferation of target cells located in media or the adventitia. However, the vascular

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responses to ionizing irradiation have not yet been fully elucidated.

The peculiar 'black hole' reported for the first time by the authors represents a proteoglycan rich plaque within the stent leading to restenosis. The significance of this finding is unknown because the number of patients studied is very small. However, it is conceivable that matrix components, being an integral part of neointimal formation, are over-expressed by radiation doses outside the 'therapeutic window'. Further studies by the authors, especially those with long-term follow-ups, will shed some light on the consequences of this finding.

What makes the P-32 stents so attractive in terms of radiation safety, is their biggest enemy: β-particle emitters produce a very steep dose fall-off at the stent margins. Stent delivery balloons are generally longer than the stents mounted on them. A steep dose fall-off is problematic, if vascular injury from i.e. a delivery balloon extends up to 2 mm beyond the margins of the stent. At the stent margins, the axial penetration of β-particles from the isotope P-32 does not reach therapeutic doses at a distance of 1 mm beyond the stent margins. Kay *et al.* therefore suggested that perhaps P-32 stents, with increased activity at the stent end ('hot-end' stents), may overcome the edge problem. However, even a fourfold increase in activity at the edge, as compared to the centre, of a 3–12 μCi P-32 stent does not allow sufficient radiation coverage of a trauma zone by a 'cold stent'-end, if this trauma exceeds a distance of 2 mm. Vascular injury outside radioactive stent margins, generally caused by balloons that are longer than stents, is the major reason for edge restenosis. One may speculate about the occurrence of edge-effects, if the region of balloon or stent injury is identical with the irradiation zone.

Other new ideas for radioactive stents include the impregnation of gamma-emitting isotopes instead of beta-particle emitters, or the self-expanding stent platform. Initial results with gamma-stents indicate that axially distributed gamma-radiation may also not be sufficient to overcome edge-effects induced by injury from a delivery balloon[13]. Encouraging results have been reported from self-expanding P-32 stents studied in a porcine model of restenosis. Self-expanding radioactive stents did not show edge-effects in this model[14]. However, these findings await further investigation in larger series and perhaps other animal models.

The angioplasty balloon impregnated with radioisotopes is a novel radiotherapy device, combining the simplicity of use of radioactive stents with the promise of a high success rate in conventional brachytherapy. It was previously shown that a balloon impregnated with radioisotopes in contact with the arterial wall not only reduces neointimal hyperplasia but also prevents constrictive vascular remodelling[15]. Thus, these impregnated balloons may not only be used for treatment of in-stent restenosis but also for de novo lesions of native coronary arteries. A number of different radionuclides, for instance isotopes used for other purposes in nuclear medicine, may be considered for an impregnation procedure. Sealed-source radioisotope balloons have the advantage over balloons filled with liquid isotopes, of minimizing the risk for contamination of patients and the environment after balloon leakage or rupture. Early results indicate that edge-effects are prevented if radioisotope balloons are used simultaneously with a dilatation procedure of the artery[15].

In summary, three very recently published clinical reports — two from Milan and the one by Kay *et al.* from Rotterdam — uniformly concluded that radioisotope stents deployed by delivery balloons do not reduce overall restenosis rates in coronary arteries because of the high incidence of edge-effects[9,16,17]. There is considerable doubt that radioactive stents will ever be resuscitated, especially if and when the rising notion of the possible success of novel drug-eluting stents to prevent restenosis is supported by convincing scientific evidence. However, vigorous testing of drug-eluting stents in pre-clinical and clinical pilot studies is mandatory, especially because drug toxicity may be a problem[18]. If these stents are safe and do not cause edge-effects, for instance by the piling up of neointimal cells outside the drug efficacy zone, then this new therapy will certainly be the option of choice for the interventional cardiologist. However, as we have learned from the story of radioactive stents, there is still room for surprise.

A. ARAB
C. BODE
C. HEHRLEIN
Department of Cardiology,
University of Freiburg,
Freiburg, Germany

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The prognosis of heart failure: the view from the real world

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Much of our understanding of the prognosis of heart failure comes from randomized clinical trials of drug therapy, which tend to recruit patients very selectively. Women, the elderly and those with co-morbidities are under-represented. There are few reports from population-based studies, with only a handful in the angiotensin-converting enzyme era. The paper by Mosterd and colleagues[1] from the Rotterdam Study is therefore an important addition to the literature.

A total of 181 subjects with heart failure were identified in a cross-sectional epidemiological study of 5540 participants aged 55 years or over, living in one suburb of Rotterdam during 1990 through to 1993. Heart failure was defined on the basis of clinical signs and symptoms and underlying cardiac abnormality on assessment (which included echocardiography in 1600 subjects). The average age of subjects diagnosed with heart failure was 77 years, more than 10 years older than those patients who typically enter clinical trials, but very much in keeping with data from recent epidemiological studies in Europe and North America[2–4]. The prognosis was grim, with a 2-year survival of only 79%, dropping to 59% at 5 years. These estimates are likely to be optimistic as only prevalent cases of heart failure were identified, and new (incident) cases of heart failure are known to have a particularly high mortality in the 3 months after diagnosis[5,6]. Even so, those with heart failure had a mortality twice that of their age-matched peers. As with the data from clinical trials, half of all the cardiac deaths were 'sudden', with a fivefold increased risk of sudden death in those with heart failure compared to their peers. The message is clear: once heart failure develops the outlook is poor, even in the era of angiotensin-converting enzyme inhibition.

Which individuals with heart failure are at particularly high risk of death? We have many reports in the literature from highly selected series of young patients with stable but severe heart failure awaiting transplantation, or from clinical trials, but few from population-based studies. The findings of the