Since the introduction of percutaneous coronary balloon angioplasty, restenosis has remained the most challenging problem facing interventional cardiologists. Stenting has reduced the need for clinically driven repeat revascularization, but has far from eliminated it. As early as 1989, intravascular brachytherapy was proposed as a means to ameliorate the proliferative component of restenosis after angioplasty. After promising results in early animal studies, brachytherapy was introduced as a treatment for the prevention of restenosis in clinical trials.1,2 This treatment was directed primarily at the very challenging subgroup of patients with in-stent restenosis.

In the present issue of Circulation Coussement et al3 describe an unfavorable 6-month outcome after catheter-based β-irradiation in a porcine coronary model. The results described may provide some insights into the biology of restenosis inhibition with brachytherapy, or they may be a finding limited by the idiosyncrasies of this particular animal model and not directly relevant to humans. In this study, normal pig coronary arteries exposed to 20 or 30 Gy of β-irradiation delivered by a 199Au liquid-filled balloon after overdilation balloon injury demonstrated greater neointimal areas and thrombosis at 6 months compared with nonirradiated vessels. On the basis of the discrepancy between the 6-month outcomes in clinical trials and these animal data, the investigators have proposed that “direct extrapolation of the long-term outcome of endovascular irradiation in the pig coronary artery preparation of restenosis to the human setting is not appropriate.”

Before we cast aside the utility of the various animal models of restenosis, we should explore the possible differences between pigs and humans, which may have produced these divergent results. One obvious explanation is that humans have an underlying atherosclerotic process, which usually manifests in the fifth or sixth decade of life, whereas balloon injury in the pig, as in the current study, is usually performed in normal arteries of juvenile animals. In addition, the primary clinical application of intracoronary brachytherapy has been directed to a group of patients with recurrent proliferative neointimal responses after prior coronary artery stenting, not the treatment of de novo lesions.

To understand further the differences between animal models and humans, it is also important to characterize fully the effects of radiation in large and small animal studies at 1 to 6 months after treatment. One-month studies in balloon-injured normal pig coronary arteries receiving radiation therapy via a source wire (β or γ), 199Au liquid-filled balloon (β-radiation), or 32P radioactive stents (β-radiation) have shown significant suppression of neointima formation associated with evidence of delayed healing. Histological analyses consistently demonstrate fibrin/platelet deposition, incomplete endothelialization, and the absence of inflammation and smooth muscle cells in irradiated vessels.4,5 Similar to the current study with 199Au liquid-filled balloons (β-radiation), we also observed arterial edge effects secondary to smooth muscle cell proliferation and proteoglycan deposition in balloon-injured arteries after radiation at 1 month (personal observations).

Carter et al.6 using 32P β-emitting radioactive stents implanted in balloon-injured atherosclerotic (cholesterol-fed for 1 month before stenting) pig coronary arteries, was the first to report greater neointimal formation at 6 months with brachytherapy compared with controls. The radioactive stents in this study had stent activities ranging from 0.5 to 12 μCi (maximum dose of 125 Gy). Initial clinical studies of the radioactive stent, however, showed a different result, with significant inhibition of neointimal hyperplasia within the body of the 32P radioactive stent at 6 months.7 Later follow-up has shown some loss of the initially favorable in-stent result at 1 year.8 The primary failure of β-particle–emitting radioisotope stents in the clinical trials, however, was related to edge restenosis in zones in which there was balloon injury with radiation dose fall-off, and not to enhanced neointima formation within the stent, as was observed in the porcine model.6,9

In another study of balloon-injured normal porcine coronary arteries, β-radiation delivered via a 32P source wire showed similar neointimal formation compared with control arteries at 6 months. In contrast, the results in humans with the same device in the same dose range produced a beneficial, not a detrimental, result at 6 months.10 These studies emphasized the importance of total dose and dose rates in producing a favorable long-term benefit.

Data from our laboratory using a rabbit iliac model also suggest that the total radiation dose and dosing rate affect the neointimal response. In rabbit iliac arteries, low-dose radiation (6 μCi 32P β-emitting radioactive stent; total dose, 95 Gy; dose rate, 19 cGy/h) resulted in less neointimal formation

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than control nonradioactive stents at 3 months but not 6 months. Higher radiation doses (24 or 48 μCi; total dose, 381 and 763 Gy; dose rate, 77 and 153cGy/h, respectively) resulted in less neointimal formation at 1 year. This benefit was lost by 2 years. These observations suggest that the delay in healing in this model is dependent on the radiation dose. This delay in healing with radiation in the rabbit is similar to that reported in the pig by Coussen et al. The persistence of fibrin, occasional hemorrhages, adherent platelets and leukocytes, and greater adventitial fibrosis all seem to be consistent with radiation therapy, and they raise concerns relating to long-term safety and efficacy.

How do we further reconcile differences between clinical and experimental studies? Another possible explanation for the conflicting results among species is that there is a differential rate of healing. This differential rate of healing may be proportional to the longevity of the species. Humans have a life span of >70 years (72.8 years for men and 79.6 years for women). In contrast, pigs have a life span of 16 years, and rabbits have a life span of 5 to 6 years. Human coronary arteries take longer to heal after injury than normal pig or rabbit arteries. Histological studies of stented human arteries show a persistence of platelet and fibrin for up to 14 and 30 days, respectively, after balloon angioplasty and stenting. Inflammatory polymorphonuclear leukocytes and macrophages are present at 1 to 3 days after stenting and persist for >3 months. T-lymphocytes appear at 2 to 3 weeks and may persist beyond 6 months. Smooth muscle cells, the main cellular component of the restenotic lesion, usually appear 14 days after stenting. The extracellular matrix, which is initially composed of proteoglycans and type III collagen, is gradually replaced by collagen type I between 6 and 12 months. In general, human coronary arteries take ~6 months to heal completely after stenting, compared with the pig coronary and rabbit iliac arteries, which heal by ~1 month, with deposition of collagen type I taking 3 to 6 months. Thus, under normal conditions (ie, no brachytherapy), human coronary arteries may take 3 to 6 times longer to heal after stenting than pigs or rabbits. This observations suggests that it is possible that the responses to γ irradiation in human arteries will eventually (ie, >3 years) be equivalent to those observed at 6 months in the porcine model.

Differential rates and magnitude of intracoronary thrombus formation and lysis may also be important contributing factors to the discrepant results observed between the porcine model and the human experience with intracoronary brachytherapy. For this reason, we have used the dog model, which is less prone to the development of fibrin-rich neointima than other models. However, we observed greater amounts of fibrin within the neointima at a mean of 110 days after 32P radioactive β-emitting stent (3 to 14.4 μCi) placement in dog coronary arteries; these results are similar to the those reported in the current study by Coussen et al. In the current study, aspirin but not ticlopidine or clopidogrel was given to the animals after very high dose (>100 Gy) brachytherapy injury to the luminal surface. In another study, Kaluza et al gave aspirin and ticlopidine to pigs for 28 days but still observed thrombotic occlusion in 2 of 10 animals treated with β-radiation and balloon angioplasty. It is possible that aspirin with ticlopidine or clopidogrel may be less able to prevent thrombosis in pigs than in humans.

Given the pro-thrombotic milieu after the mechanical and radiation injury, it is not surprising that the authors observed evidence of “repeated thrombotic episodes” contributing to the neointimal response in their model. Even without radiation injury, pig coronary arteries are more prone to thrombus-driven neointimal hyperplasia that observations in this model led some investigators in the 1980s to propose that recurrent layering of thrombus was the primary driver of neointimal hyperplasia and restenosis in humans. This concept may be more applicable in pigs than in humans, however, because heparin therapy has failed to reduce neointimal formation. The failure of heparin-coated stents to inhibit neointimal hyperplasia in humans also suggests that myofibroblast cellular proliferation may be more important than thrombus formation as the primary driver of restenosis.

Finally, how do we put the current study in an appropriate perspective for the practice of interventional cardiology? First, it is clear that for patients with in-stent restenosis, both γ- and β-irradiation–based intracoronary brachytherapy offer reasonably safe and effective means to reduce the risk of further in-stent restenosis. In multiple controlled and randomized clinical trials, the beneficial results for this clinically challenging patient group are apparent at 6 months and, in a small subset of patients, for 3 years. The broader application of intracoronary brachytherapy for high risk de novo lesions should be discouraged until late safety and efficacy outcomes can be validated in carefully controlled clinical trials. Although delayed thrombosis is clearly a risk after the clinical application of intracoronary brachytherapy, this risk seems to be minimized with prolonged (>6 to 9 months) antiplatelet therapy with aspirin and either clopidogrel or ticlopidine. If one equates 1-month studies in the pig to the 6-month follow-up in humans, then the published brachytherapy animal studies have correlated with clinical outcomes with intracoronary radiation in patients. However, the findings from the current study and others suggest that we may eventually see evidence of late restenosis (“catch-up”) in some patients. If this risk exists, it needs to be kept in perspective, because all of our catheter-based treatments to treat atherosclerotic coronary disease are palliative and not curative. If and when these patients present with late recurrent restenosis, revascularization with bypass surgery or, in the not too distant future, drug-eluting stents, should be considered. It is thus incumbent on us to continue efforts to reduce, reverse, or prevent the systemic disease of atherosclerosis.

References


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