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Articles

ß-Particle–Emitting Stents Radiate Enthusiasm in the Search for Effective Prevention of Restenosis

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Introduction

Renarrowing of a coronary artery (restenosis) at the site of earlier balloon angioplasty is in 1996 still a clinical problem, with an incidence of 30% to 50%. Despite 20 years of experimental and clinical research, the biology of restenosis is still not fully understood. These studies have, however, greatly enhanced our insight into the restenosis process. The most widely accepted concept is that restenosis is the result of the vascular healing response to the injurious treatment. This response includes several phases: elastic recoil, thrombosis, inflammation, proliferation, and organization (or remodeling). Application of therapies aimed at reducing restenosis according to this paradigm has been partially successful. One approach involves the limitation of the thrombotic phase by effectively blocking the platelet glycoprotein IIb/IIIa receptor[1] (preliminary results from the CAPTURE and EPILOG studies support this approach). In these studies, the need for repeated coronary revascularization was substantially reduced but not eliminated. A second approach is the use of coronary stents. By limiting the residual lesion, elastic recoil, and late remodeling, stents reduce the need for both revascularization and angiographic restenosis[2,3] compared with balloon angioplasty.

Results from more recent nonrandomized studies with stents suggest that an improved deployment technique and/or the use of ticlopidine improve the efficacy of coronary stenting.[4,5] However, restenosis rates remain written in two-digit numbers. Combination of the antithrombotic

approach with coronary stents is currently in clinical trials.

The use of heparin-coated stents was shown to be feasible and safe in the pilot study of the Benestent II trial.[6] Patient recruitment in the Benestent II randomized study, which compared the efficacy of heparin-coated Palmaz-Schatz stents with balloon angioplasty, is completed, and final results will be available in late 1996. A second multicenter clinical trial has been initiated that compares the efficacy of conventional noncoated stents with and without the concomitant use of the platelet glycoprotein IIb/IIIa antibody ReoPro (the ERASER trial). Results of this study are expected in 1997.

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Fibrocellular tissue (neointimal proliferation) is an important component of the restenotic lesion after balloon angioplasty and is almost the sole contributor to restenosis after stent implantation. This fibrocellular tissue is derived from proliferating myofibroblasts surrounded by newly synthesized extracellular matrix. The histologic picture of this tissue is very similar to keloid scars and smooth muscle cell (SMC) tumors. Therefore, radiation therapy has been used by several investigators to reduce the extent of neointimal proliferation.

One of the first studies to apply external beam x-ray irradiation in a porcine coronary model showed unexpected accentuation of neointimal proliferation.[7] In more recent studies, several research groups have shown the efficacy of catheter-based endovascular γ- or ß-irradiation in rabbit iliac, porcine iliac, and porcine coronary models.[8] [9] [10] Regardless of the type of radioactive source at doses >10 to 18 Gy, these studies showed a marked reduction in the number of intimal SMCs and the thickness of the tissue layer. This effect was sustained at 6 months.[11] [12]

Preliminary clinical studies have begun in human iliac restenotic lesions,[13] human AV hemodialysis shunts,[14] and human coronary lesions. A group in Frankfurt, Germany, treated ≈30 patients with recurrent iliac restenosis with γ-radiation (12 Gy). Follow-up of up to 5 years showed no clinical restenosis (personal communication, D. Liermann, Atlanta, Ga, 1996), but the angiographic follow-up was incomplete. In the SCRIPPS study, 55 patients were assigned randomly to either 8- to 25-Gy γ-radiation or the use of a cold catheter after coronary angioplasty. This trial was stopped by the US Food and Drug Administration pending investigation device exemption approval of the device. Follow-up results of the enrolled patients are awaited. A group in Caracas, Venezuela, treated 22 patients with 20- to 25-Gy γ-irradiation after coronary angioplasty. Follow-up is incomplete, but so far 4 patients with restenosis and 7 patients with aneurysm-like coronary dilatation have been identified (personal communication, J.A. Condado, Atlanta, Ga, 1996). Finally, a group at the University Hospital Geneva (Switzerland) treated 15 patients after coronary angioplasty with 8- to 18-Gy ß-irradiation. This group reported 100% procedural success with no cardiac events at 30 days. Six-month follow-up will be complete later this year (personal communication, P.M. Urban, Rotterdam, Netherlands, 1996).

Advantages and Disadvantages of Catheter-Based Endovascular Radiation

Provided that the potential benefits of endovascular radiation therapy will be proved in clinical studies in the near future, several pros and cons need to be considered. Obviously, the fact that catheter-based endovascular radiation therapy is quickly applied (2 to 10 minutes) after the angioplasty procedure and does not require long-term drug use or a permanent implant is an advantage. That the use of γ-irradiation is a disadvantage for application in the coronary system has been recognized by most workers in the field. For instance, the total body dose of delivering 10 Gy within 2 minutes by use of ^{192}Ir (γ) is estimated to be 10 000 mSv compared with 5 mSv with ^{90}Sr (ß). Obviously, the radiation protection measures need to be more extensive when a γ source is used. An important part of the procedure is the care taken to deliver the required dose to the vessel wall. New centering devices are being designed to provide uniform dosimetry distributed evenly to the intima, media, and adventitia. Eccentric residual lesions make this task difficult. Another issue especially relevant for low-penetrating ß-sources is the level in the vessel wall at which the effective dose should be delivered for restenosis reduction. Recent data suggest that the adventitial myofibroblasts contribute significantly to coronary renarrowing in a porcine overstretch injury coronary model[15] and therefore may be the preferential target.

Radioactive Stents

Recently, the efficacy of ß-particle radiation from stents was shown in cultures of animal and human SMCs[16] and in rabbit iliac arteries.[17] Fischell et al[16] showed that 0.2-mm titanium wires impregnated with a very low concentration of ^{32}P (hot) inhibited the growth of cultures of a rat and human SMCs in a zone 5 to 10 mm around the wires. Nonradioactive ^{31}P (cold) showed no effect on SMC proliferation. Hehrlein et al[17] showed that neointimal formation in a rabbit iliac model after implantation of ^{32}P-containing short Palmaz-Schatz stents was significantly reduced at 4 and 12 weeks. In this issue of *Circulation*, Carter and colleagues[18] report another study that evaluates the short-term effects of ß-particle–emitting short stents compared with regular stents in normal porcine coronary arteries.

Compared with earlier animal studies with catheter-based endovascular radiation in porcine coronaries or radioactive stents in rabbit iliacs, the results are surprising. Stents with low or high activity showed only a modest treatment effect of ≈30% reduction in neointimal area compared with "cold" stents. However, stents with a medium activity (1 μCi) showed a 200% increase in neointimal area.

We cannot exclude that there is a U-shaped dose-response curve for endovascular radiation, but in view of all the earlier reports, this is unlikely. The interactions between radiation dose and vessel wall cellular elements are complex, but so far incremental doses have always resulted in

more cell death or decreased cell proliferation. It may be that the increase in neointimal area is a reflection of the higher injury scores in this subgroup (see Table 1 of Reference 18). If confirmed, these data may be regarded as the first crack in the mirror for radioactive stents because dosimetry would therefore be very difficult, if not impossible.

Another important topic relevant to the study by Carter and colleagues[18] is the duration of follow-up. Like cancer radiotherapy, sparing some proliferating cells may only delay, not eliminate, regrowth. As was shown recently by Hehrlein et al,[17] low-activity radioactive stents may show efficacy at 4 weeks (like the 4-µCi stents in their studies), but longer follow-up to 12 weeks revealed that most of that effect was lost. Therefore, the data shown in the study by Carter et al[18] need confirmation with longer follow-up.

If confirmed in future studies and human trials, radioactive stents may have an advantage over catheter-based radiation: dosimetry. Because under ideal conditions stents are nicely apposed to the vessel wall, less variability will occur in the dose between different points around the circumference of the stent and between the three layers of the vessel wall, provided that the residual lesion is minimal. Uniform radioactivity over the entire stent is a prerequisite to ensure homogeneous targeting of the arterial wall. This requirement, however, is not yet fulfilled with the stent used by Carter and colleagues (see Fig 1 of Reference 18).

The benefits of "pure" ß-emitting stents seem obvious. Exposure of nontarget organs of the patient and the catheterization laboratory personnel is minimal. Storage of stents in the laboratory requires less shielding. On the downside, if someone drops a stent on the floor, a pure ß-emitter would be hard to locate. Perhaps the addition of a very small amount of a γ-emitting isotope would be safer in this instance.

Footnotes

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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