Fulfilling the Promise of Percutaneous Angioplasty

Paul S. Teirstein, MD

It is ironic that in 1964, Dotters’ initial application of percutaneous transluminal angioplasty (PTA) targeted femoral-popliteal stenoses.1 Now, nearly 4 decades later, although angioplasty has gained wide acceptance as a first-line treatment for diseased coronary, iliac, and renal arteries, its role in femoral-popliteal vessels remains controversial and poorly defined. The initial PTA procedure is nearly always a success. Improved technology, including slick guidewires, sleek balloons, and sinuous stents can reliably open most femoral-popliteal obstructions. However, one cannot attempt angioplasty in the lower legs without running into its Achilles heel: restenosis. In contradistinction to angioplasty in the coronary, iliac, and renal vasculature, restenosis rates after lower-extremity PTA are unacceptably high. The femoral-popliteal system has unique anatomic and physiological properties. Blood flow rates are low, resistance is high, and lesions are often very long, with poor run-off. These characteristics raise the risk of recurrence to well over 50%, and in some reports, over 80%.2,3 Alternative surgical approaches using saphenous and prosthetic grafts provide better long-term patency but cause significantly more morbidity.4 Often, patients with peripheral vascular disease also have cardiac, cerebrovascular, and/or renal disease that increases the risk of major surgery. Although surgery is often embraced for limb salvage, surgery for the treatment of claudication is generally avoided. It is not surprising, therefore, that so many vascular medicine specialists currently recommend conservative medical therapy and walking programs as a first-line treatment for symptomatic femoral-popliteal disease.

Over the past decade, much has been learned about the mechanism of restenosis. There are 2 major components of restenosis: the first is the mechanical renarrowing of the dilated region; the second is the biological proliferative response to injury.5,6 Percutaneous angioplasty is a purely mechanical intervention. In recent years, our mechanical tools have improved considerably. Careful quantitative angiography has taught us that using these new tools to optimize the initial luminal dimension can reduce restenosis by mitigating the consequences of intimal hyperplasia. Stents, for example, provide a mechanical scaffolding that opens the lumen wide and limits recoil. Thus, stents reduce restenosis predominantly by allowing the lumen to better accommodate the ingrowth of neointimal tissue.7 Stents, however, do not reduce, and in fact actually increase, the proliferative response to injury. Clearly, mechanical solutions alone will never eliminate restenosis. An effective solution requires targeting both the mechanical obstruction and the biological response to injury that results in neointimal tissue growth within the lumen.

In this issue of Circulation, Minar et al8 provide the first scientific evidence, in the form of a double-blind, randomized trial, that endovascular γ-radiation can reduce restenosis after PTA of femoral-popliteal disease. When 113 patients with long-segment femoral-popliteal lesions were randomized to either the γ-emitter 192Ir or placebo, restenosis at 6-month follow-up was 53.7% in placebo compared with 28.3% in treated patients (P<0.05). Cumulative patency at 12 months was 35.3% in the placebo versus 63.6% in the treated group (P<0.005). Similar improvements were noted in the ankle-brachial index and the peak velocity ratio. Radiation was successful despite enrollment of an extremely heterogeneous and, in many cases, high-risk patient population, including very lengthy de novo, recurrent, stenotic, and occluded lesions. Although 2 small registries previously also documented high patency rates after γ-radiation of femoral-popliteal disease,9,10 the power of the present study is its double-blind, randomized design. Despite the small sample size of the study, highly significant differences were observed between the treated and placebo groups. Thus, by use of PTA to treat the mechanical component of restenosis and then adjunctive radiation to target the biological component, for the first time, an acceptable long-term clinical outcome was achieved.

This report adds considerably to the growing body of evidence that radiation therapy is an effective anti-restenosis treatment.11 Recently, γ-radiation has proved efficacious for the treatment of coronary artery restenosis in 3 separate, double-blind, randomized trials.12–15 On the basis of these data, on June 19, 2000, a US Food and Drug Administration panel voted unanimously to recommend approval of γ-radiation to treat in-stent native coronary artery restenosis. Several recent randomized trials have also proved positive for the β-emitters 90Y, Sr/90Y, and 32P.16,17

In addition to its positive angiographic, noninvasive, and clinical findings, the present report also highlights several caveats important to the implementation of vascular radiation therapy. First, the protocol entry criteria wisely excluded the use of stents. Recent data from several coronary radiation
trials point to a strongly unfavorable interaction between radiation and freshly implanted stents.\textsuperscript{18,19} It appears that radiation prevents cell growth so powerfully that endothelialization of newly implanted stents is inhibited, leaving stent struts relatively bare for an extended time period. Therefore, in the absence of prolonged anti-platelet therapy, the presence of freshly implanted stents at the time of irradiation increases the risk of late stent thrombosis. In the present study, no stents were implanted during the radiation procedure, and late thrombosis was not observed.

Second, in some coronary radiation studies, the beneficial anti-restenosis effect of radiation within the treated segment was reduced at follow-up by the presence of new narrowings at the lesion margins. This so-called “edge effect” was most pronounced in studies using the $^{32}$P radioactive stent.\textsuperscript{20,21} Edge effect is believed to be due to endovascular injury incurred by the angioplasty procedure that extends outside of the irradiated region. Common recent practice, therefore, is to provide an adequate margin of radiation at either end of the treated (ie, injured) vessel segment. In the present study, the investigators used a very wide, 10-mm radiation margin, and no edge effects were observed.

Third, in Figure 3 of their article, the authors provide angiographic images from a case of radiation failure. Although this patient clearly sustained recurrent restenosis after radiation, the length of the recurrent stenotic segment was significantly shorter than the initial stenosis. This phenomenon of a “partial response” has also been observed in coronary radiation studies and is relevant because of the well-known improved long-term outcome when shorter versus longer lesions are subjected to repeat angioplasty.

Fourth, it should be recognized that although in the present study restenosis rates at 6 months were improved by 47%, there were still many radiation failures. Radiation is not a “cure-all,” and some patients who receive this new therapy with high hopes will be profoundly disappointed. Our failures, however, do provide us with the opportunity for improvement. For example, in this study, 12 Gy was prescribed at 3 mm from a noncentered source. Perhaps a higher dose will improve efficacy. Delivery of higher doses, however, must be approached cautiously. Delivery of a higher dose with the noncentered delivery system used in this study might result in excessive radiation exposure to the vessel wall actually making physical contact with the delivery catheter. A more sophisticated delivery system, such as the centering device currently under investigation in the Peripheral Artery Radiation Investigational Study (PARIS) trial, will improve dose homogeneity and may more safely allow prescription of a higher dose.\textsuperscript{22}

Finally, it should be observed that although the 12-month results described in this report are extremely encouraging, longer follow-up of these patients, as well as patients in other vascular radiotherapy trials, is essential to document the durability and long-term safety of this new technology. It will also be important to document that late failures, if and when they occur, do not result in further clinical deterioration due to regression or elimination of critical collateral blood supply. An effective anti-restenosis therapy will most likely have a major impact on percutaneous revascularization. In particu-


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