

# An Update on Peripheral Brachytherapy

Vascular brachytherapy still plays a role in the current treatment of restenosis.

BY RON WAKSMAN, MD, FACC

**B**ecause the manifestation of coronary atherosclerosis and peripheral arterial disease (PAD) is primarily evident in older patient populations, and because patients in the baby boomer generation are nearing their 60s, the full impact of peripheral and coronary atherosclerosis in the US is upon us. Whereas coronary vascular procedures increase at a rate of 8% per year, there is greater growth in the frequency of peripheral procedures, estimated at 19% per year. Despite new advances such as stents, including drug-eluting stents (DESs), atherectomy devices, thrombectomy and endoluminal grafts, the restenosis rate after peripheral artery intervention continues to compromise the overall success of these procedures.

Restenosis is still considered the Achilles' heel of percutaneous endovascular intervention.<sup>1-8</sup> Among the approaches for the prevention and treatment of restenosis in the peripheral arterial system (PAS), only vascular brachytherapy (VBT) is reported to be safe and effective in a selected group of patients (patients with superficial femoral artery [SFA] lesions and renal artery in-stent restenosis). VBT is not approved for marketing for clinical use, but it is used either as an investigational device or on a compassionate use basis. This article reviews the status of VBT, the available systems and dosimetry for use, and provides a summary of the latest reports from the clinical trials utilizing VBT to prevent or treat restenosis in the PAS.

## RESTENOSIS IN THE PAS

Restenosis after PTA is mainly seen in small and medium peripheral arteries, such as the saphenous

femoral-popliteal arteries and renal arteries, with diffuse atherosclerotic disease. The mechanisms for a high rate of recurrence after intervention in the PAS are mainly attributed to exuberant healing response with smooth muscle proliferation,<sup>8,9</sup> early and late recoil after balloon angioplasty,<sup>10,11</sup> mechanical problems

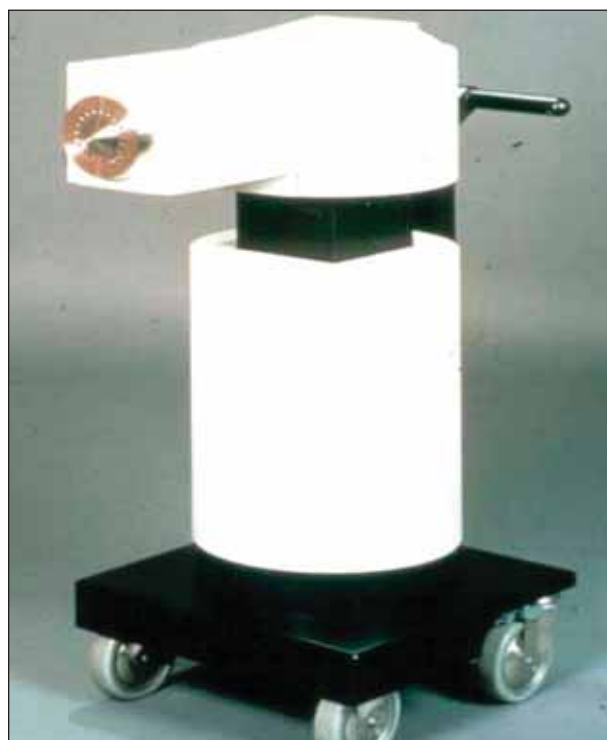


Figure 1. The MicroSelectron HDR afterloader (Nucletron-Odelft, Delft, The Netherlands).

with stents, such as stent fractures and crushing, in-stent restenosis, and aggressive progression of the atherosclerotic disease.

Despite significant advances in techniques and equipment, there has not been much progress in combating this high recurrence rate after intervention. DESs have the potential application in peripheral arterial occlusive disease.<sup>12</sup> Thus far, however, the data generated from the latest trials using the sirolimus-eluting nitinol stent (the SIROCCO study) demonstrate late recurrences and mechanical problems with the stents. The primary endpoint of the study was the in-stent mean percent diameter stenosis, as measured by quantitative angiography at 6 months. The in-stent mean percent diameter stenosis was 22.6% in the sirolimus-eluting stent group versus 30.9% in the uncoated stent group ( $P=.294$ ).<sup>13</sup>

The SFA is one of the most heavily diseased vessels in the body: occlusion is common, and there is often poor distal runoff, which creates a high resistance and a low-flow state. The reported 3- to 5-year patency rates for the endovascular treatment of femoropopliteal disease are as low as 38% to 58%.<sup>1,7</sup> With the dissemination of stent use in the SFA and for the treatment of renal artery stenosis, we are experiencing an acceleration in the rate of in-stent restenosis rates in the peripheral system, which continues to be a challenge for therapy. Other peripheral sites affected by restenosis include bypass graft anastomoses and arteriovenous dialysis grafts, and after the placement of transjugular intrahepatic portosystemic shunts (TIPS). Carotid arteries have low rates of restenosis; however, when restenosis does occur, it is resistant to conventional therapy and tends to recur aggressively.

## THE STATE OF VBT IN 2004

VBT is a promising technology with the potential to reduce restenosis rates. Clinical trials to evaluate the effectiveness and safety of this technology are strong, with nearly 5,000 patients enrolled in these trials.<sup>14-18</sup> These trials led the approval for marketing of two beta systems using P-32 and Sr/Y90 emitters and one gamma radiation system using Ir-192. These studies demonstrate different levels of efficacy and raise further questions regarding proper dosimetry, the incidence of edge effect, the late thrombosis phenomenon, and late restenosis. Five-year follow-up of clinical and angiographic data collection on patients treated with intracoronary radiation for the prevention of restenosis has recently been released and showed overall safety, with a modest degree of late recurrences, but overall superior outcomes when compared to control.<sup>19</sup> In

2004, two commercial systems were taken off the market, leaving the BetaCath system (Novoste Corporation, Norcross, GA), with the beta source Sr/Y90, as the only available radiation system currently used for vascular application.

The use of VBT for the treatment of in-stent restenosis decreased significantly during the past year because of the dramatic reduction in restenosis rates in the coronary tree due to the introduction and use of drug-eluting stents.<sup>20,21</sup> For in-stent restenosis in bare-metal stents, operators prefer the use of DESs over VBT to avoid the logistics involving radiation oncology in the cath lab.<sup>22,23</sup> Thus, VBT is gradually becoming a niche device for refractory restenosis in patients who failed with DESs or who have diffuse in-stent restenosis. Outside of the coronary tree, there is compelling evidence to support the use of VBT for preventing primary or secondary restenosis when a patient has suffered DES failure. However, there is no radiation system approved for use in the peripheral system, and the dosimetry calculations have not been clearly established.

## RADIATION SYSTEMS FOR THE PERIPHERAL VASCULAR SYSTEM

The vessel size of the PAS favored the use of gamma radiation due to the penetration characteristics of the emitter. The majority of investigational work performed in the PAS used Ir-192 in doses of 14 Gy to 18 Gy prescribed at 2 mm from the source center. Several radiation systems for peripheral endovascular brachytherapy have been suggested and are under development and testing.

## External Radiation

External beam radiation is a viable option for the treatment of peripheral vessels. It allows a homogenous

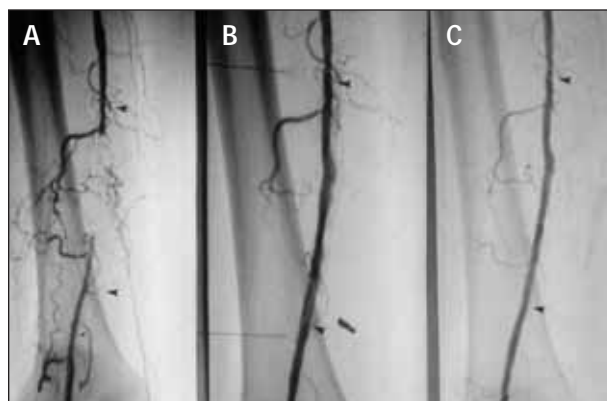


Figure 2. A patient from the Vienna brachytherapy trials before PTA (A), after PTA (B), and after 12 months (C).

TABLE 1. SFA RADIATION TRIALS

Study	No. of Pts.	Randomized	Centered Cath.	Dose (Gy)	@ mm	Patency Control %	Patency VBT %
Frankfurt	30	—	—	12	3	—	82
Vienna 1	10	—	No	12	3	—	60
Vienna 2	113	Yes	No	12	r+0	—	72
Vienna 3	134	Yes	Yes	18	r+2	46	77
Vienna 4	33	No	Yes	14	r+2	—	79
Vienna 5	98	Yes	Yes	14	r+2	45	88*
Bern II for Restenotic Lesions	100	Yes	—	12	r+2	58	77
PARIS Pilot	40	No	Yes	14	r+2	—	88
PARIS Randomized	203	Yes	Yes	14	r+2	80	76
Swiss 4-Arm Study	346	Yes	Yes	12	r+2	58	83

\*Excluding the thrombosis cases.

dose distribution with the possibility of fractionation. External radiation is currently used in a few centers for treating in-stent restenosis of the SFA. Preliminary reports are encouraging, although caution should be applied to this strategy because of the potential for radiation injury to the nerve, vein, and the skin. Preliminary attempts with external radiation for the treatment of AV dialysis grafts failed to reduce the restenosis rate. This unsuccessful attempt was attributed to the conservative use of low doses and thrombosis of these grafts. Using stereotactic techniques to localize the radiation to the target area may improve the results of this approach.

### Catheter-Based Gamma Systems

The most common catheter-based system used for SFA application is the MicroSelectron HDR system (Figure 1), which uses a computerized, high-dose rate afterloader system that delivers a 3-mm stepping, 10-Ci activity of Ir-192 into a closed-lumen radiation catheter. The Peripheral Brachytherapy Centering Catheter (Paris, Guidant Corporation, Indianapolis, IN) is a 7-F, double-lumen catheter with multiple centering balloons near its distal tip that enable the catheter to be centered in the lumen of large peripheral vessels during inflation. The Paris catheter is no longer available. The only closed-end lumen catheter available is the one used for oncology applications.

### Catheter-Based Beta Systems

The only catheter-based beta system available is the

BetaCath system, with a source train of up to 60 mm, which can be pulled back to allow coverage of long lesions. The main limitation of the system is the penetration of the beta emitter, which is weakened significantly beyond 5 mm. This system can be used for below-the-knee applications or for other small vessels, including in-stent renal stenosis. It is recommended to administer the radiation before the intervention to ensure better centering and a higher dose to the treated proliferating tissue.

Other innovative catheter-based radiation system developments have been halted because of the declining interest in the VBT field or slow recruitment into clinical trials. Included among these halted developments was the Radiance balloon system (Radiance Medical Systems, Irvine, CA), which was particularly attractive for peripheral applications because it is associated with apposition of a solid beta P-32 source attached to the inner balloon surface into the surface of the vessel wall. Another approach was the use of low x-ray energy delivered intraluminally via a catheter. The emitter was 5 mm in length and 1.25 mm to 2 mm in diameter and could be administered distally to the lesion and pulled back to cover the entire lesion length. The Corona system, a modification of the BetaCath system, was used to accommodate beta systems with the Sr/Y90 emitter in the peripheral system. In this system, the balloon was filled with CO<sub>2</sub>, allowing centering and preventing dose attenuation. A clinical study in the SFA for in-stent restenosis lesions entitled MOBILE was ter-

minated because of poor enrollment. The Corona system was also used in the BRAVO (beta radiation following balloon angioplasty for improving life span of recurrent failed arteriovenous fistulae) study for patients with AV dialysis grafts.

CLINICAL TRIALS

SFA

Liermann and Schopohl were the first to perform VBT to treat in-stent restenosis in the peripheral arteries. Known as the Frankfurt Experience, this pilot study was conducted in 30 patients with in-stent restenosis in their SFAs.<sup>24-27</sup> Patients underwent atherectomy and PTA followed by endovascular radiation using the MicroSelectron HDR afterloader and a noncentering catheter with Ir-192. No adverse effects from the radiation treatment were reported at up to 7-year follow-up. The 5-year patency rate of the target vessel was 82%, with only 11% stenosis within the treated segment reported. Late total occlusion developed in 7% of treated vessels after 37 months.

The Vienna Experience

A series of studies was conducted at the University of Vienna. Most of these were randomized studies targeting the SFA with or without stents using the

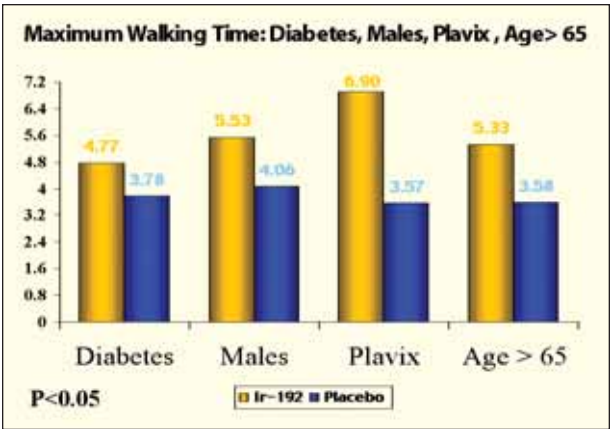


Figure 3. Subanalysis of the PARIS study.

MicroSelectron HDR afterloader with or without a centering catheter utilizing different doses. The results of these studies are displayed in Table 1.

Vienna I was a pilot study with an indication of radiation safety after PTA that showed only 60% patency at 1 year.<sup>28</sup> The Vienna II trial had 113 patients with *de novo* or recurrent femoropopliteal lesions who were randomized to PTA + brachytherapy (n=57) or PTA alone (n=56) (Figure 2). The primary endpoint of cumulative patency rates at 12-month follow-up was

higher in the PTA + brachytherapy group (63.6%) compared to the PTA group (35.3%). The patients from this study were followed-up to 36 months and demonstrated durability of the results.<sup>29</sup> In Vienna III, a centering catheter that was used for the same patient population with a dose of 18 Gy showed a restenosis rate of 23.4% in the irradiated group compared to 53.3% in the placebo arm.<sup>30</sup> Vienna IV was a pilot study examining radiation with stenting of the SFA; and Vienna V was a randomized study for similar indications. Both Vienna IV and V demonstrated an increased rate of subacute and late thrombosis when stents were combined with radiation, with up to 16.7% in the radiation group versus 4.3% in the control stenting without radiation. Once thrombosis was controlled, the radiation group had less restenosis.<sup>31</sup>

### The PARIS Trials

The Paris Radiation Investigational Study (PARIS) is the first FDA-approved, multicenter, randomized, double-blind control study involving 300 patients following PTA to SFA stenosis using VBT with Ir-192 (Figure 3). Utilizing the MicroSelectron HDR afterloader, a treatment dose of 14 Gy is delivered via a centered segmented end-lumen balloon catheter. The primary objectives of this study are to determine angiographic evidence of patency and a reduction of >30% of the restenosis rate of the treated lesion at 6 months. A secondary end-point is to determine the clinical patency at 6 and 12 months by treadmill exercise and by ankle-brachial index (ABI). In the feasibility phase of PARIS, 40 patients with claudication were enrolled. The mean lesion length was  $9.9 \pm 3$  cm, with a mean reference vessel diameter of  $5.4 \pm 0.5$  mm. The 6-month angiographic follow-up was completed on 30 patients; 13.3% of them had evidence of clinical restenosis.<sup>32</sup>

Because of poor enrollment, only 203 patients with

claudication and femoropopliteal disease were enrolled in the study. After successful PTA, a segmented centering balloon catheter was positioned to cover the PTA site. The patients were transported to the radiation oncology suite and randomized to receive either radiation therapy using the MicroSelectron HDR afterloader with Ir-192 at a dose of 14 Gy at 2 mm into the vessel wall (105 patients), or treatment with a sham control in 98 patients. Patients were followed for 12 months, with clinic visits at 1, 6, and 12 months, and follow-up angiography at 12 months. The restenosis rate at follow-up was similar in both groups (28.6% brachytherapy vs 27.5% placebo). There was no significant difference in minimal lumen diameter (MLD), late loss, or the number of total occlusions. Exercise ABI, resting ABI, and maximum walking time were not different between treatment groups. For patients older than 65 years, maximum walking times at 6 and 12 months were better in the brachytherapy group. In the subgroups of patients with diabetes, males, or those receiving clopidogrel or who had a proximal/medial lesion, maximum walking time in the brachytherapy group was better than in the placebo group at 6 months but not different at 12 months.

More studies to support the effectiveness of gamma radiation for in-stent restenosis were recently published by Krueger et al.<sup>33</sup> In this study, 30 patients who underwent PTA for *de novo* femoropopliteal stenoses were randomly assigned to undergo 14 Gy centered endovascular irradiation (irradiation group, n=15) or no irradiation (control group, n=15). Intra-arterial angiography was performed 6, 12, and 24 months after treatment; and duplex ultrasonography was performed the day before and after PTA, and at 1, 3, 6, 9, 12, 18, and 24 months later. Baseline characteristics did not differ significantly between the two groups. Mean absolute individual changes in degree of stenosis, compared with the

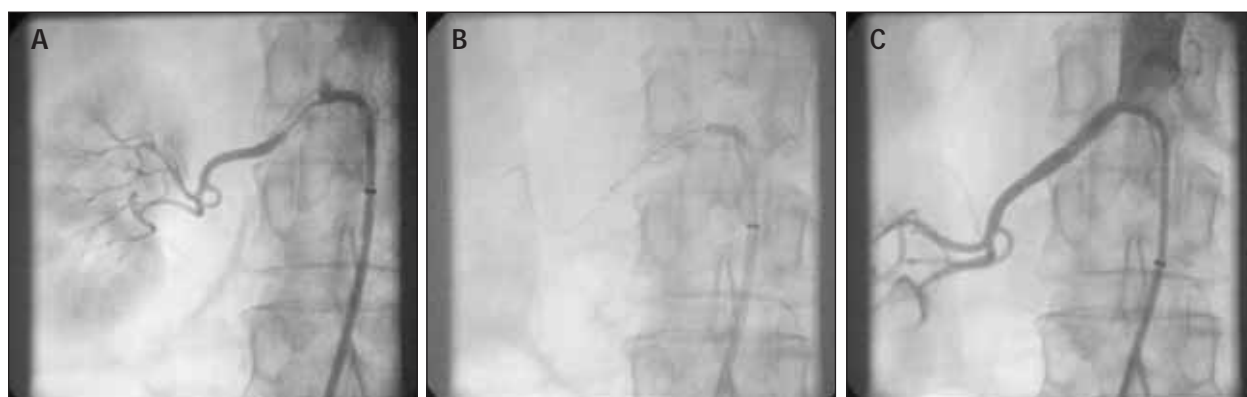


Figure 4. In-stent renal artery stenosis treated with gamma radiation. In-stent restenosis in 20% renal stents (A). Ribbon with Ir-192 seeds prior to PTA (B). Angiographic follow-up at 6 months (C).



degrees of stenosis shortly after PTA in the irradiation group versus in the control group were  $10.6\% \pm 22.3$  versus  $39.6\% \pm 24.6$  ( $P < .001$ ) at 6 months,  $2\% \pm 34.2$  versus  $40.6\% \pm 32.6$  ( $P = .002$ ) at 12 months, and  $7.4\% \pm 43.2$  versus  $37.7\% \pm 34.5$  ( $P = .043$ ) at 24 months. The rates of target lesion restenosis at 6 months ( $P = .006$ ) and 12 months ( $P = .042$ ) were significantly lower in the irradiation group. The investigators concluded that endovascular radiation was effective for patients who were treated with angioplasty for *de novo* femoropopliteal lesions.

### Restenotic Lesions and VBT

The effectiveness of VBT for restenotic SFA lesions was examined in another randomized study reported by Zehnder et al. In this study, gamma radiation was used at a dose of 12 Gy. The primary endpoint was  $>50\%$  restenosis at 12 months assessed by duplex Doppler. The recurrence rate in the radiation arm was 23% versus 42% in the PTA alone group.<sup>34</sup> This study demonstrated that VBT can be effective in restenotic lesions.

### Brachytherapy and Probucol

In another randomized four-arm study for patients with PTA lesions, patients were randomized to VBT, VBT and probucol, probucol alone, or placebo. The recurrence rate in the radiation arm alone was 17%, VBT and probucol was 20%, probucol alone was 27%, and the placebo group was 42%. This study confirms previous observations regarding the effectiveness of VBT for the treatment of SFA lesions without additional benefit of probucol when compared to PTA alone.<sup>35</sup>

### Studies With Beta Radiation for SFA Stenosis

Two studies that used the Corona system were the MOBILE study that targeted in-stent restenosis lesions and the LIMBER (Limb Ischemia Treatment and Monitoring post Vascular Brachytherapy to prevent Restenosis) study.

### AV DIALYSIS STUDIES

In 1994, an initial study at Emory University to treat patients who had failed PTA of arteriovenous dialysis grafts using the MicroSelectron HDR afterloader reported a 40% patency rate at 44 weeks,<sup>36</sup> however, the long-term results of this study were similar to stand-alone PTA without radiation. Nori et al reported similar disappointing results in a pilot study utilizing external radiation doses of 12 Gy and 18 Gy for AV dialysis shunts in 10 patients.<sup>37</sup> At 6 months, target lesion revascularization was 40%, but at 18 months, all grafts failed and required intervention. Cohen et al ran-

domized 31 patients to PTA or stent placement alone, followed by external radiation of 14 Gy in two 7-Gy fractions and reported restenosis rates of 45% versus 67% in the irradiated and control groups, respectively, at 6 months.<sup>38</sup> New studies are currently underway using low-dose external radiation to reduce restenosis of vascular access for AV grafts in hemodialysis patients, as are other studies using a centering device to deliver an accurate homogenous dose of radiation after PTA. BRAVO was a pilot study utilizing the Corona system with an Sr/Y90 beta emitter. In the study of 10 patients with an average of 3.9 previous angioplasties to their AV graft, there was 60% primary patency and cumulative patency of 80% at 12-month mean follow-up.<sup>39</sup>

### Radiation for Renal In-Stent Restenosis

Several investigators reported on the efficacy of gamma radiation for the treatment of in-stent renal stenosis.<sup>40,41</sup> The most recent report comes from Washington Hospital Center in which gamma radiation was used in 10 consecutive patients who presented with renal in-stent restenosis. The radiation was performed prior to PTA and the patency rate at 12 months was 90% (Figure 4).

Other reports for the use of VBT in the PAS include the SCRIPPS experience in which endovascular radiation therapy was utilized to prevent restenosis after TIPS for patients with portal hypertension. Overall, the restenosis rate due to intimal hyperplasia of TIPS at 6 months has been reported to be as high as 70%. Complete thrombosis as early as 2 weeks after the procedure has been reported.<sup>42</sup> Several case reports suggest that VBT can be effective for the use of in-stent restenosis of carotid arteries.

### LIMITATIONS OF BRACHYTHERAPY

Although clinical trials using VBT for both coronary and peripheral applications have demonstrated positive results in reducing restenosis rates, these trials have also identified two major complications related to the technology—late thrombosis, especially in the presence of stents<sup>43</sup> and edge stenosis. Late thrombosis is probably due to the delay in healing associated with radiation. It has been demonstrated that late thrombosis can be remedied through the prolonged administration of antiplatelet therapy after intervention. The main explanation for the occurrence of edge effect is a combination of low doses at the edges of the radiation source and an injury created by the device for intervention that is not covered by the radiation source. It has been shown that wider margins of radiation treatment

to the intervening segment significantly reduce the edge effect.

## FINAL COMMENTS

With the growing popularity of peripheral vascular medicine, identifying a reliable treatment for the plaguing recurrence of restenosis will increase and augment the benefits of vascular intervention. Investigators have shown that the endovascular delivery of radiation therapy is one such treatment. Combating restenosis in the peripheral vascular system is contingent upon understanding the processes, mechanisms, and potential targets affected by brachytherapy use. The successful outcome of clinical trials in the coronary arteries facilitated recognition of VBT to become standard of care for the treatment of in-stent restenosis. Expansion of the indications to *de novo* lesions identified the potential, but also the limitations, of the technology. Simultaneously, investigators embarked on a series of studies using VBT as adjunctive therapy for intervention in peripheral arteries. The outcome of these trials will determine the future role of VBT as a tool for prevention of restenosis in the peripheral vascular system. ■

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