Local Application of Beta-Particle Radiation to Reduce Venous Anastomotic Intimal Hyperplasia in Polytetrafluoroethylene Arteriovenous Fistulas

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ABSTRACT

The long-term patency of arteriovenous fistulas (AVF) created for hemodialysis is limited, especially when prosthetic implants such as polytetrafluoroethylene (PTFE) are used. Since intimal hyperplasia (IH) at the venous anastomosis is the most common cause of AVF demise, a therapeutic technique to safely diminish this hyperplastic response would be valuable to dialysis patients. Recently, pure beta-emitting stents were shown to be effective in decreasing IH in coronary arteries after angioplasty. This study was designed to assess the ability of a newly developed beta-emitting external foil to inhibit IH at the venous anastomosis in PTFE AVFs in a canine model.

Bilateral PTFE bridge graft AVFs were placed from the femoral artery to vein in adult mongrel canines. A metallic stainless-steel foil coated with the beta-emitter rhenium 188 was placed around the venous anastomotic site of one AVF in each animal. Twelve weeks after AVF implantation each animal was sacrificed and samples of each anastomosis analyzed histologically.

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(Abstract continued)

Eight venous anastomoses were analyzed (four test and four control). An analysis of neointimal hyperplasia was performed with image analysis software. Although not statistically significant, there was a trend toward diminished IH observed in the irradiated versus control anastomoses (132.36 ± 36 μ vs 159 ± 22 μ). However, a foreign-body response was noted external to the vein and anastomosis on the implant side, leading to decreased diameter in the irradiated versus control veins (1.52 ± 0.21 mm vs 3.80 ± 1.02 mm).

Venous IH may be attenuated in canine PTFE AVFs with the use of an external beta-emitting foil. Further larger studies to determine the ideal dosimetry and implant material to maximize vein contact yet minimize foreign body response are necessary. This technology could result in a safe and effective way to improve performance in AVFs.

Introduction

The long-term patency of AVFs created for hemodialysis in patients with renal failure is limited, especially when prosthetic graft material such as polytetrafluoroethylene (PTFE) is used. The patency rates for such grafts are usually measured in months.1-3

Most of these graft failures have been attributed to myointimal hyperplasia at the venous outflow anastomosis. The neointima that forms at this site consists of rapidly proliferating smooth muscle cells.1,4,5 There is no clinically useful therapy for the suppression of this proliferation.

Several recent reports have demonstrated that radiation therapy after angioplasty or stent implantation in the coronary arteries potentially inhibits IH.6-10 Early studies used either external beam irradiation or endovascular afterloading with gamma radiation sources.6-8,11 The use of gamma radiation in this setting is somewhat impractical owing to safety issues, prolonged radionuclide half-lives, and extended time of exposure often needed for results.12,13

Recently, to overcome the shortcomings of gamma radiation, pure beta-particle-emitting stents have been shown to be effective in decreasing IH in vitro and in animal models.10,12,14 The benefit of beta emission is that more than 99% of the radiation is absorbed within 5 mm of the source, thus eliminating any significant risk of radiation toxicity to patient or personnel.10

To date, the most commonly used beta emitter has been phosphorus 32. Problems with phosphorus 32 include the need for stents to be acti- vated far in advance of actual deployment and the 14-day half-life. Rodent experiments have shown that the irradiation of arteries between 1 hour before and 3 days following angioplasty is most efficacious.10,15,16 Therefore, rhenium 188, a beta emitter with a half-life of 17 hours and a tissue penetration of about 3 mm, would seem to be a better choice. Its half-life would allow 94% of the radiation dose to be delivered within the first 3 days of application.15

The process of IH that occurs in coronary arteries after angioplasty or stenting is similar to that which occurs at vascular anastomoses in PTFE AVFs, and so radiotherapy may be effective in this setting also. As of yet, no major study has assessed the ability of beta radiation to diminish IH occurring at vascular anastomoses. The objective of this study was to evaluate the ability of a newly developed beta-emitting external foil of rhenium 188 to reduce IH at the venous anastomosis of PTFE AVFs. The choice of the venous anastomosis is ideal owing to the high rate of graft failure at the venous anastomosis as well as the thin vein wall, which allows easy beta-particle penetration.1,4,5

Methods

Implant Preparation

The beta-emitting foils were prepared according to a method used to prepare radioactive rheni- um 188 stents, using slight adaptations necessary
because of the larger size of the foils. \(^{17}\) The carrier-free radioisotope rhenium 188 was obtained from a tungsten 188/rhenium 188 generator\(^ {18}\) by eluting with saline, concentrating the radioactivity on a SepPak QMA column and taking it up into the 0.44 M cobalt plating solution in 1 M boric acid of pH 4.

Stainless steel 302FH foils of 12.7 \(\mu\)m thickness and sized 3 cm by 4 cm were electroplated with radioactive rhenium 188 at a current density of 87 A/m\(^2\) for 5 minutes by submersing the foil in 4 mL of the rhenium 188 solution containing about 12–15 mCi. The foil was rinsed and further coated with a 2 \(\mu\)m gold layer. The plating solution for this purpose was phosphate-buffered 0.07 M KAu(CN)\(_2\) (Alfa Aesar) at a pH of 7.0, and plating was conducted at 50 A/m\(^2\). The rinsed foils were air dried and their activity measured in a calibrated RadCal ionization chamber. Each foil was placed in a glass petri dish and autoclaved before implantation into the dogs. The average amount of activity per foil was 332 \(\mu\)Ci at the time of implantation.

The radioactive rhenium 188 foils have been dosimetrically evaluated by gafchromic film dosimetry. Gafchromic film is a thin, almost colorless polyester sheet embedding a chromophore that turns dark blue under the influence of radiation. \(^{19}\) Gafchromic film was calibrated with 6-MV photon doses ranging from 0 to 200 Gy within 1 day of measurement. A stack of six 0.26-mm-thick and 4 \(\times\) 6 cm\(^2\) pieces of gafchromic film type MD-55 (Nuclear Associates, Carle Place, NY) was placed on the radioactive foil and put between two pieces of tissue-equivalent plastic material ("solid water," RMI 457, Gammex, Middleton, WI). The radioactive foil was left in place for 13 hours. The irradiated gafchromic film samples and the calibration pieces were scanned together at 300 dpi on an Epson 636 scanner with transparency unit to obtain the radiation dose distribution curve. All measured doses within 5 mm of the edge of the foil were averaged and the "dose delivered until complete decay" calculated by dividing the measured doses with 0.41143 (Figure 1).

### Animal Experiment

The animal work was approved by the animal care and utilization committee of Northeastern Ohio Universities College of Medicine. All animal care was in accordance with the "Guide for the Care and Use of Laboratory Animals" (Office of Science and Health Reports CPRR/NIH, 1996). Adult mongrel canines were prepared for surgery by withholding food for 12 hours before surgery. At the time of surgery, cefazolin 1 g IV was administered, and sodium pentothal (15–25 mg/kg IV) was used as an induction agent. The canines

![Figure 1](image.png)

**Figure 1.** Radiation doses delivered by the gold-coated rhenium-188 foil. The activity of the foil was normalized to the experimentally used activity of 332 \(\mu\)Ci at the time of implantation and the dose calculated until complete decay.
were maintained on isoflurane for general anesthesia. The animals were placed in dorsal recumbency, and 6 centimeters of femoral artery and vein were isolated. Systemic anticoagulation was achieved with IV heparin (100 U/kg). Bilateral AVFs were constructed by using standard wall 4 mm PTFE in an end-side anastomosis with CV-6 Gore-Tex suture (Figure 2). The radioactive implant was randomly assigned to one venous anastomosis in each dog and held in place with 2-0 silk sutures (Figure 3). Wounds were closed with 2-0 Vicryl. All animals were allowed to recover and returned to care facilities. Animals were maintained on a normal laboratory diet and received 81 mg aspirin each day for 5 days. All animals were euthanized 12 weeks after surgery with fatal-plus solution 10 cc IV.

Pathology, Graft Isolation, and Data Evaluation

Post-mortem, grafts were isolated, and flushed with heparinized saline followed by 10% buffered formalin. Following removal, the venous anastomosis was longitudinally sectioned and processed with hematoxylin-eosin and Verhoeff Mason's Elastin/Trichrome staining. Keyence video microscope (Keyence Corp., Osaka, Japan) with Global Lab image analysis software (Data Translations, Marlboro, MO) with 20× magnification was used to evaluate the inflammatory response around the vessel as well as vein lumen diameter. Similarly, with 50–200× magnification, the Verhoeff-Mason's Elastin/Trichrome slides were evaluated for intimal thickening at several sites in the region of the anastomosis. Final gross and histologic analysis was done on eight venous anastomoses from four dogs. Four test grafts and four control grafts were analyzed.

Results

Keyence video microscope with Global Lab image analysis software was used to quantitate the extent of inflammatory response to the implant by measuring the outer wall thickness of the gross specimen. An external inflammatory response occurred in the implant specimens, causing the outer wall to measure 2.91 ± 1.52 mm on test veins versus less than 1 mm on all control veins (p < 0.002) (Figure 4). This inflammatory reaction led to decreased vein lumen diameter of 1.52 ± 0.21 mm on the irradiated versus 3.80 ± 1.02 mm on the nonirradiated veins (p < 0.057).

Histologic evaluation included longitudinal sections through the venous anastomosis with hematoxylin-eosin and Verhoeff-Mason Elastin/Trichrome staining. Keyence video microscope with Global Lab image analysis software was used to measure IH at several sites of the bypass. The irradiated AVFs showed diminished neointima versus the control AVFs (Figure 5). Average inti-
mal thickening was $132 \pm 36 \mu m$ in the test vein versus $159 \pm 22 \mu m$ in the control vein. For IH, further statistical testing was not applied owing to unequal variance and small sample size. The average IH in the region of the toe was $130 \pm 20 \mu m$ versus $155 \pm 13 \mu m$ and in the region opposite the toe was $136 \pm 54 \mu m$ versus $163 \pm 32 \mu m$ (irradiated versus nonradiated). Once again owing to small sample size and unequal variance, further statistical analysis was not applied.

**Discussion**

This study is the first to evaluate the use of externally applied beta radiation to vascular anastomoses to attempt reduction of IH. The venous anastomosis of a PTFE AVF was chosen for two reasons: (1) the failure of PTFE AVFs is most commonly due to IH at the venous anastomosis, and (2) the minimal thickness of a vein wall is ideal for allowing beta-particle penetration.$^{1,4,5,17}$

![Figure 4.](image1.png)  
**Figure 4.** Gross appearance of venous anastomosis showing foreign-body response and decreased vein lumen around test vein (A) vs control vein (B).

![Figure 5.](image2.png)  
**Figure 5.** Trichrome photomicrograph demonstrates diminished intimal hyperplasia in test vein (A) vs control vein (B).
The implant that was developed for this project consisted of a 302FH stainless steel foil of 0.0005 inch thickness loaded with rhenium 188 and overplated with gold. The choice of rhenium 188 as a radioactive source was based on its safety and ease of use. Beta-emitters are 99% absorbed within 5 mm of their source and thus present minimal handling risks and minimal risk to the patient.\textsuperscript{10,17}

In fact, precautions at the time of surgery consisted mainly of surgical gloves. In addition, rhenium 188 is a favorable choice because of its short half-life, which allows delivery of 94% of the radioactive dose within the first 3 days of application, a time that has been shown to be the ideal for radioactive IH inhibition.\textsuperscript{10,15,16} Furthermore, the process by which the implants were made required less than 15 minutes, and each implant was made radioactive at the time of surgery.

The final histologic analysis of IH in this study was promising. A trend toward decreased IH was clearly demonstrated in the irradiated veins. The major concern was the intense inflammatory reaction surrounding the test veins, which actually compressed the vein lumen diameter. Such an inflammatory reaction could decrease graft outflow and diminish the life of the AVF, thereby eliminating any benefit from decreased IH. Unfortunately, it is impossible to ascertain if the beta radiation or the implant itself was responsible for the reaction since no implant was placed around the controls. If it is assumed the reaction was mainly a simple foreign-body response, this problem could be overcome by using another implant material employing a different final coating or even embedding the radioactive source in the PTFE.

The use of radiotherapy in coronary arteries and in association with angioplasty has recently been extended to clinical trials and shows promising results.\textsuperscript{13} So far, little attention has been focused on using this same technology in the reduction of IH at vascular anastomoses. This might be partly due to a perception that the radiotherapy must be delivered within the vessel as well as the concern about disruption of the anastomosis by radiotherapy. Although not conclusive, this study suggests that externally placed beta sources at vascular anastomoses can decrease IH without disruption of the anastomosis. Larger studies are necessary to determine the ideal dosimetry to decrease IH as well as to find an ideal implant material that will allow close approximation to the vein without causing such a severe inflammatory response. This technology could result in a safe and effective adjunct to decrease IH in PTFE AVFs, thus potentially increasing patency rates.

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References


