

# Repeated Intracoronary Beta Radiation for Recurrent In-Stent Restenosis

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More than 70% of percutaneous coronary interventions are followed by a stent implantation. In-stent restenosis still occurs in 20–30% of patients and remains a therapeutic challenge. At present only vascular brachytherapy has been shown to be an effective treatment option. We report here one case of recurrent in-stent restenosis after vascular brachytherapy that was successfully treated by a second beta radiation treatment.

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**Key words:** in-stent restenosis; vascular brachytherapy; cutting balloon; angioplasty

## INTRODUCTION

Intracoronary stents improve clinical and angiographic outcomes when compared with balloon angioplasty, as shown in BENESTENT and STRESS trials [1,2]. Today, in most hospitals, more than 70% of percutaneous coronary interventions are followed by a stent implantation.

However, in-stent restenosis still occurs in 20%–30% of patients and remains a therapeutic challenge [1,2]. At present, only vascular brachytherapy (VBT) has been shown to be an effective treatment option [3]. Nevertheless, this therapy is not 100% effective and recurrent in-stent restenosis after brachytherapy occurs. We report here one case of recurrent in-stent restenosis after VBT that was successfully treated by a second beta radiation treatment.

## CASE REPORT

A 67-year-old white female was first admitted to our hospital in 1997 for angina associated with dyspnea and dizziness. Her past medical history was negative except for hyperlipidemia and tobacco consumption. Physical examination was unremarkable. In view of her symptoms, she subsequently underwent cardiac catheterization without a prior stress test. Selective coronary angiography revealed two-vessel disease with a tight stenosis of both the circumflex (LCx) and the right coronary arteries (RCA). The left ventriculogram showed a normal ejection fraction. A double angioplasty with stent implantation of the LCx (NIR 3.5/9 mm, Boston Scientific, Natick, MA) and of the RCA (Angiostent 3.5/35 mm, Angiodynamics, Queensbury, NY) was carried out. The stent implanted in the RCA was deployed at 8 atm. The hospital course was uneventful, but 4 months later chest

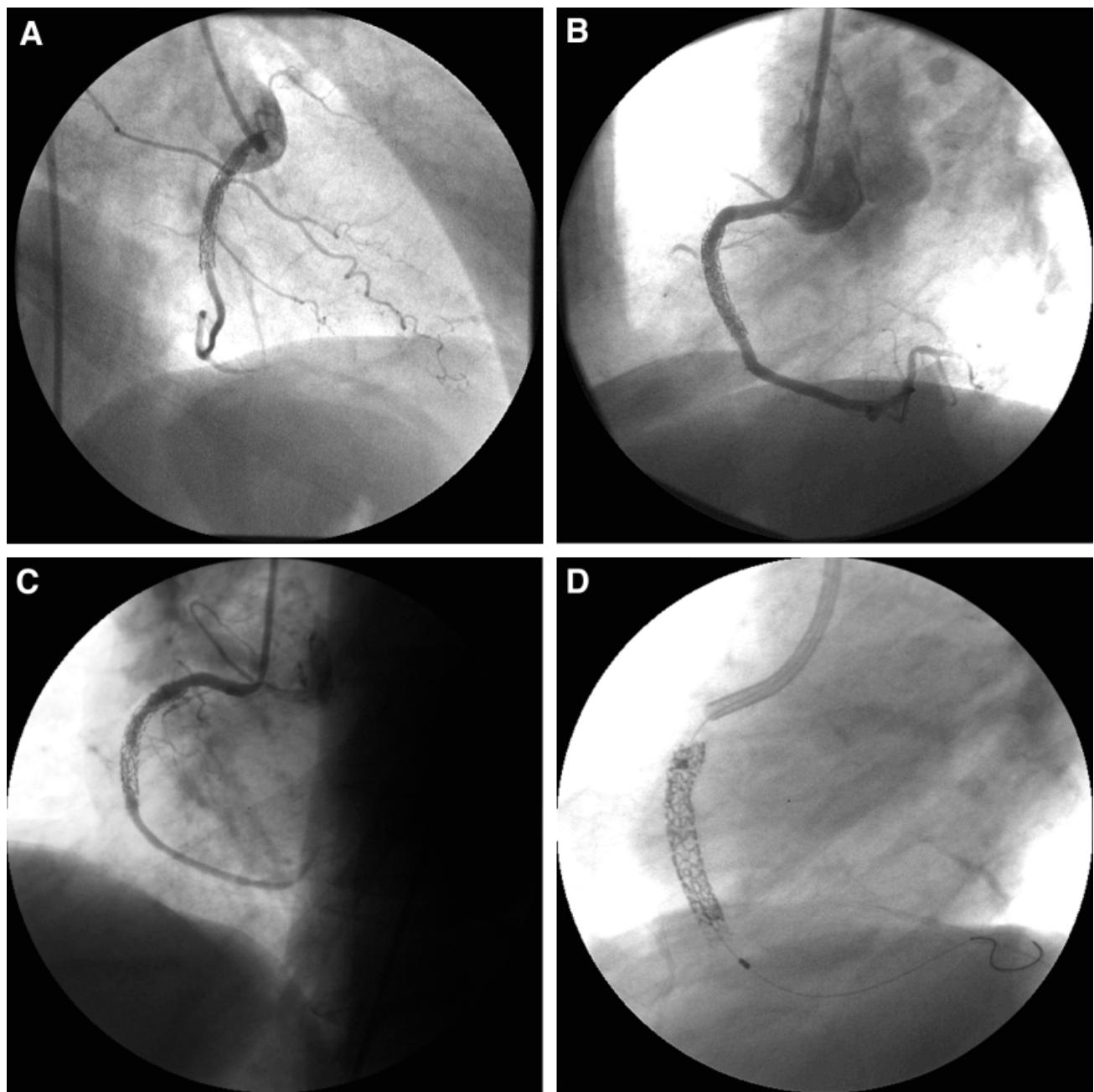
pain recurred and a stress test was positive. A repeat angiogram showed a widely patent CX stent but a diffuse, proliferative in-stent restenosis on the RCA that was successfully treated by conventional balloon angioplasty only (4.0/20 mm balloon). The patient did well but after 3 months chest pain recurred and a new stress test was positive. The angiogram showed a new diffuse restenosis in the distal part of the stent of the RCA. This was again treated by balloon angioplasty with a good angiographic immediate result. Four months later, angina symptoms recurred and were complicated this time by congestive heart failure. The angiogram showed an in-stent restenosis in the distal part of the stent (Fig. 1A). A new balloon PTCA was performed, followed by VBT using a 30 mm long <sup>90</sup>Sr/Y beta-emitting source (Beta-Cath, Novoste) delivering 20 Gy to 2 mm from the source with an excellent final result (Fig. 1B). However, 3 months later, a new angiogram, performed because of the abrupt onset of unstable angina 2 weeks after the ticlopidine was stopped, showed a late thrombotic occlusion that could be successfully treated by further balloon angioplasty and the reintroduction of long-term treatment with clopidogrel. Symptoms recurred 8 months later and a new diffuse in-stent restenosis (Fig. 1C) was treated

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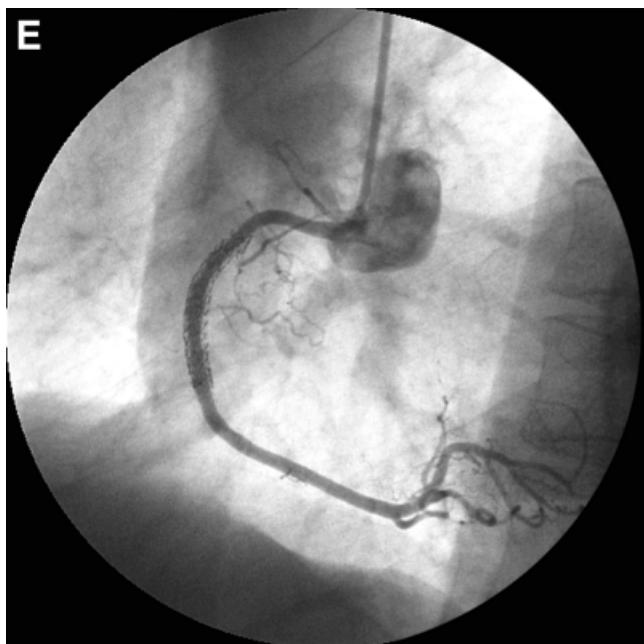


**Fig. 1.** A: Coronary angiogram showing a significant in-stent restenosis in the right coronary artery. B: Final result after balloon angioplasty followed by beta radiation. C: A new in-stent restenosis is present after the first brachytherapy treatment. D: Position of the 30 mm source train (between the radiopaque markers) within the delivery catheter, with adequate overlap of the restenotic segment. E: No significant restenosis at the 7-month follow-up angiogram.

with a cutting balloon 4.0 mm in diameter and 10 mm long followed by a second VBT using a 30 mm long  $^{90}\text{Sr}/\text{Y}$  source (Novoste) delivering 22 Gy at 2 mm from the source (Fig. 1D). Seven months later, the patient was free of symptoms and a final angiogram showed an excellent result (Fig. 1E).

## DISCUSSION

Proliferative in-stent restenosis remains a therapeutic challenge for the interventional community. Several patterns of in-stent restenosis have been described, the occlusive form being the most difficult to treat [4]. Balloon



**Figure 1 (Continued.)**

angioplasty [5], balloon angioplasty followed by a new stent [6], rotablation [7], cutting balloon angioplasty [8], and other techniques are often unsuccessful, especially in diffuse forms of restenosis. Only VBT has been shown to be highly effective to treat this iatrogenic entity either with a gamma [3,9,10] or a beta source [11,12]. In these different studies, restenosis rate (taking into account the entire segment, not only the initial lesion) decreased from 50%–55% in the placebo (PTCA) to 15%–20% in the irradiated arm.

Since 1998, we have been performing VBT in our institution as the treatment of choice for in-stent restenosis. We describe here a patient with a very symptomatic and aggressive form of in-stent restenosis that recurred despite several attempts with balloon angioplasty. Surgery was not considered because of the patient's preference and because of single RCA involvement.

A first treatment with beta radiation was given but a new restenosis occurred. After reviewing the angiogram, it was clear that the 30 mm long beta source had entirely covered the whole segment that was injured by the balloon and that geographical miss has not occurred. We then postulated that an insufficient dose of radiation was delivered to the vessel wall and therefore irradiated the vessel a second time. The procedure was preceded by balloon angioplasty with a cutting balloon. A second dose of 22 Gy at 2 mm from the source, calculated from the quantitative angiographic measurements, was delivered and the immediate result was excellent. The patient was free of angina and an elective 7-month follow-up

angiogram showed the absence of restenosis. Moreover, there was no coronary aneurysm, a side effect described when using high dose of radiation [13].

Several trials have shown that gamma brachytherapy is very effective for the treatment of in-stent restenosis. Gamma radiation has a superior depth-dose gradient compared with beta source. It is therefore possible that a noncentered beta source applied in a big vessel (3.5 mm in our patient) delivers a suboptimal dose of radiation to the deep vessel wall (media and adventitia), which could explain occasional failure of this treatment. However, the BETA WRIST trial [14] suggests that beta radiation is also effective for in-stent restenosis, which has been confirmed by the recent results of the START and INHIBIT trials [11,15].

The optimal dose of radiation to prevent restenosis is still unknown. The recent study by Verin et al. [16] utilizing beta radiation for de novo lesions suggests that 18 Gy at a tissue depth of 1 mm not only prevents the renarrowing of the lumen but actually induces luminal enlargement (positive remodeling). The present case suggests that an insufficient dose may be one of the cause of VBT failure. It is well known that the angiogram often underestimate the true vessel size. We therefore have changed our policy from 1999 on and calculate the dosimetry to deliver from the intravascular ultrasound measurements. Since the targets of radiotherapy are the smooth muscle cells localized in the media and the adventitia, intravascular ultrasound measurements may allow an optimal dosimetry. This may explain occasional treatment failure when the dosimetry is based on quantitative angiographic measurements alone.

To our knowledge, this is the first report of a repeated VBT treatment for in-stent restenosis with a cumulative dose of 42 Gy (prescribed at 2 mm of depth) administered over 7 months. Even though it is difficult to compare the dose delivered by different systems and isotopes, in the first human study conducted by Condado et al. [13], a dose between 19 and 55 Gy was prescribed in de novo or restenotic lesions. Two subacute thrombosis (9%) and four pseudoaneurysms (18%) were reported during the early follow-up but extended follow-up to 5 years has not been associated with any further unexpected side effects (J.A. Condado, personal communication).

Subacute thrombosis after radiotherapy can be the consequence of a delayed reendothelialisation and has been linked to a new stent implantation [10]. However, clinical data have so far not shown any relationship between the dose administered and the subsequent occurrence of late thrombosis [16]. It is possible that high doses of radiotherapy can increase the incidence of coronary pseudoaneurysm [13] and/or late stent malapposition.

Longer-term clinical and angiographic follow-up in this case are obviously needed. Large-scale dose-finding studies with longer follow-up (5 years) seem imperative since the recent approval by the FDA of two devices for the delivery of radiation opens the route to the diffusion of this new technique in many catheterization laboratories throughout the world.

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