

## SCIENTIFIC LETTER

# Repeated $\beta$ irradiation for failed intracoronary radiation therapy in patients with in-stent restenosis

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Vascular brachytherapy (VBT) is the only proven treatment option for patients with in-stent restenosis. In seven randomised trials with almost 1500 patients that evaluated  $\gamma$  (five studies) and  $\beta$  (two trials) irradiation, target vessel failure reduction ranged from 73% to 34% by VBT compared with conventional angioplasty.<sup>1</sup> However, the reported restenosis rates with the active treatment still varied between 17% and 32%.<sup>1</sup> We therefore postulated that repeat VBT is safe and efficacious for preventing refractory in-stent restenosis in high risk patients with failed VBT.

## METHODS

Beginning in January 1999, VBT was applied for all patients with in-stent restenosis. VBT was systematically performed with intravascular ultrasound (IVUS) guidance. The repeat procedure was performed with a strontium/yttrium-90 source train (BetaCath, Novoste, Norcross, Georgia, USA). The design and application of this catheter have been described previously.<sup>2</sup> The dosimetry was based on the manufacturer's recommendations but taking into account not the angiographic vessel reference diameter but the external elastic membrane diameter (as determined by IVUS). The mean dose delivered at 2 mm from the source centre was 23.3 (2.2) Gy during the index procedure and 25.3 (2.2) Gy during the repeat intervention. Percutaneous coronary intervention (PCI) was performed according to standard clinical practice.

Failed VBT was defined as angina recurrence combined with target vessel failure (as documented by any repeat angiography: premature depending on early symptom recurrence or at the planned six month control). Repeat VBT was considered for patients estimated to be at high risk for refractory in-stent restenosis or if they had a prognostic risk—that is, diffuse or ostial in-stent restenosis or total occlusion, or proximal left anterior descending artery stenosis. Focal edge effect stenoses and non-prognostic lesion locations in symptomatic patients were treated by conventional PCI. Written informed consent was obtained from all patients before intervention. The study was approved by the hospital ethics committee. All VBT patients were prospectively entered in a dedicated database by a person not taking part in the interventions.

A combined antiplatelet treatment (aspirin 100 mg and clopidogrel 75 mg daily) was prescribed for at least six months after the index procedure and for one year after the second VBT. Control angiography was mandatory at six months in all VBT patients and systematic long term clinical follow up was carried out.

## RESULTS

Between July 1998 and March 2003, 251 VBT interventions were performed at our institution: 22 patients were treated for primary restenosis prevention and 229 patients for in-stent restenosis. VBT failed in 34 patients (14.8%); 23 underwent conventional PCI and 11 underwent repeat VBT. The baseline clinical and angiographic demographics were

comparable for both groups. Concerning the repeat VBT group, mean (SD) age was 60 (7) years, nine patients were men, and two had diabetes. All patients who underwent a repeat procedure had incapacitating angina pectoris. Angina recurred at 7 (2) months (range 4–10) after the first, failed VBT. The restenosis pattern (table 1) was diffuse in the majority of patients at the first presentation and remained diffuse with exacerbation to total occlusion in two patients. In the focal restenosis group, two patients had ostial in-stent restenosis. The cause of recurrent in-stent restenosis was an evident geographical miss in two patients (a focal and a diffuse pattern case). IVUS and angioplasty were successful before irradiation therapy in all patients. During repeat VBT, a 40 mm source train was used in seven patients and a pullback technique was required in two because of the length of the restenotic segment. No additional stents were implanted and no evidence of geographical miss was seen at repeat intervention. Table 1 shows quantitative coronary angiography and IVUS data. During the index procedure, the minimum in-stent luminal area increased from mean (SD) 5.8 (1.8) to 7.5 (1.4) mm<sup>2</sup>. This area was maintained at the repeat intervention at 7.8 (2.1) mm<sup>2</sup> and further expanded to 8.9 (1.8) mm<sup>2</sup>. All repeat interventions were technically successful and there were no adverse clinical events during the in-hospital phase.

All patients underwent control catheterisation at six months and no patients were lost to clinical follow up. The mean follow up time was 24 (8) months (range 17–40 months). Angiography showed a patent stent without restenosis in all patients. In particular, no angiographic complication (aneurysm formation) was observed. Nevertheless, one patient had bypass surgery at another hospital because of significant disease of the left anterior descending artery (which was not the irradiated artery). During further follow up, two late events occurred. One patient had symptomatic restenosis at 12 months and one woman with angina recurrence presented with an occlusive restenosis at 22 months.

## DISCUSSION

This study describes the complete long term angiographic and clinical outcomes of a homogeneous group of patients with recurrent in-stent restenosis with failed  $\beta$  VBT and who underwent a second VBT. The results show the feasibility of the technique and indicate an excellent outcome at six months with absence of recurrence or any angiographic complication. Nevertheless, during late follow up late refractory restenosis occurred in two of 11 patients at one year and beyond.

IVUS was systematically performed in all patients. Baseline IVUS showed an average minimum in-stent strut luminal area of 5.8 (1.8) mm<sup>2</sup> indicating suboptimal stent expansion

**Abbreviations:** IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; VBT, vascular brachytherapy

**Table 1** Qualitative, quantitative angiographic, and ultrasound data

Restenosis pattern	Repeat intervention		Conventional intervention	
	First	Second	First	Second
Focal	4	4	6	13
Diffuse	7	5	15	6
Occlusion	0	2	2	4

  

Angiographic analysis	Index procedure	Repeat intervention	Follow up
Reference diameter (mm)			
Before	3.21 (0.39)	3.27 (0.46)	NA
After	3.33 (0.50)	3.48 (0.51)	3.39 (0.47)
Minimum lumen diameter (mm)			
Before	0.89 (0.47)	0.73 (0.46)	NA
After	2.67 (0.48)	3.08 (0.49)	2.73 (0.47)
Diameter stenosis (%)			
Before	79 (21)	82 (18)	NA
After	19 (8)	11 (4)	18 (7)

  

Ultrasound analysis	Index procedure	Repeat intervention
Distal reference area (mm <sup>2</sup> )	7.1 (1.5)	7.3 (1.1)
Proximal reference area (mm <sup>2</sup> )	8.8 (1.80)	9.1 (2.2)
Stenosis lumen minimum area (mm <sup>2</sup> )	4.4 (1.0)	4.2 (1.0)
Initial stent strut minimum area (mm <sup>2</sup> )*	5.8 (1.8)	7.8 (2.1)
Final stent strut minimum area (mm <sup>2</sup> )*	7.5 (1.4)	8.9 (1.8)

Data presented as mean (SD).

\*Minimum surface within the stent struts.

NA, not applicable.

in proportion to the proximal and distal reference segments. Previous reports have highlighted the “mechanical” contribution to in-stent restenosis.<sup>3</sup> Castagna and colleagues<sup>3</sup> observed a minimum stent strut luminal area below 6 mm<sup>2</sup> in 38% of 1090 patients presenting with in-stent restenosis. In the present study, this area was increased to 7.5 (1.4) mm<sup>2</sup> at the index procedure and further expanded to 8.9 (1.8) mm<sup>2</sup> during the second VBT. Compared with the initial VBT, slight increases in the proximal and distal reference IVUS diameters were observed at the repeat VBT, which was concordant with a small increase in reference diameters on quantitative coronary angiography. This may explain the slightly higher radiation dose during the second intervention.

VBT has been established as the only efficacious treatment for diffuse in-stent restenosis.<sup>1</sup> However, a failure rate between 10–30% with recurrent in-stent restenosis has been reported.<sup>1</sup> The angiographic restenosis recurrence pattern is mostly focal and may respond well to conventional PCI. This is confirmed by the present observation of an excellent outcome of patients treated by conventional stenting for focal lesions.

The rate of recurrent target vessel revascularisation after PCI for failed VBT has been reported to range between 32–33.3%.<sup>4</sup> We therefore defined angiographic inclusion criteria for repeat VBT in patients considered to be at high risk for recurrent failure. Recently, Waksman and colleagues<sup>5</sup> reported their initial experience with repeat VBT for recurrent in-stent restenosis. At nine months’ follow up, the target vessel revascularisation rate was significantly lower after repeat VBT than after conventional PCI (23.5% v 54.6%) and the authors concluded that repeat VBT was safe and efficacious in the short term. The present long term observation somehow attenuates this message, as late clinical events occurred at up to 22 months. Furthermore, a major limitation of the work of Waksman and colleagues<sup>5</sup> is that the true proportion of patients with pure refractory in-stent restenosis was not reported. Indeed, a substantial number of patients might have been included in primary restenosis

prevention trials (consisting of radiation therapy and definite stenting of a primary lesion).

The present study is limited by its observational character and the low number of patients. However, it concerns a more homogeneous population treated in a systematic manner with a complete long term follow up.

In conclusion, repeat  $\beta$  irradiation for refractory in-stent restenosis in patients with failed VBT is safe and feasible with excellent mid term results. This intervention may be considered as a treatment option taking into account the risk for late failure, as unexpected and late recurrent in-stent restenosis beyond one year may occur. Therefore, the role of this treatment needs to be further determined.

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