

## INTERVENTIONAL CARDIOLOGY AND SURGERY

# Clinical and angiographic acute and follow up results of intracoronary $\beta$ brachytherapy in saphenous vein bypass grafts: a subgroup analysis of the multicentre European registry of intraluminal coronary $\beta$ brachytherapy (RENO)

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**Objective:** To assess clinically and angiographically the feasibility, safety, and effectiveness of vascular brachytherapy (VBT) in saphenous vein bypass grafts (SVG).

**Patients and methods:** 67 of 1098 (6.1%) consecutive patients of the European registry of intraluminal coronary  $\beta$  brachytherapy underwent treatment for 68 SVG lesions by VBT using a Sr/ $^{90}$  source train (BetaCath). Clinical follow up data were obtained for all of them after a mean (SD) of 6.3 (2.4) months and angiographic follow up was performed in 61 patients (91.0%) after 6.9 (2.0) months.

**Results:** 58 (86.6%) patients were men, their mean (SD) age was 66 (10) years, 28 (41.8%) had unstable angina, and 21 (31.3%) had diabetes. Fifty three (77.9%) lesions were in-stent restenosis, 13 (19.1%) de novo lesions, and 2 (3.0%) non-stented restenotic lesions. Mean (SD) reference diameter before the intervention was 4.19 (0.52) mm, mean (SD) lesion length was 23.56 (20.38) mm, and mean (SD) minimum lumen diameter measured 0.73 (0.62) mm. Mean (SD) acute gain was 3.02 (0.88) mm. The prescribed radiation dose was 20.1 (3.2) Gy. Pullback manoeuvres were performed in 17 (25.0%) of cases. Most patients received combined aspirin and thienopyridin treatment for 6 or 12 months after the procedure. Technical success was obtained in 62 (91.2%) treated lesions and in-hospital major adverse cardiac events occurred in 4.5%. At follow up, mean (SD) reference diameter was 4.20 (0.53) mm, minimum lumen diameter 2.94 (1.50) mm, and late loss 0.86 (1.25) mm. The overall major adverse cardiac events rate was 26.7%.

**Conclusion:** VBT of SVG is feasible and safe. At follow up the reintervention rate and cardiac morbidity and mortality seem to be favourable, considering that interventions in SVG usually are associated with the highest risks.

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The treatment of patients with obstructive disease of coronary artery bypass grafts (CABG) is challenging. Within a decade after surgery, half of all saphenous vein bypass grafts (SVG) have severe atherosclerotic disease.<sup>1-4</sup> Management of graft disease is problematic, since repeated surgery entails substantial risk.<sup>5-6</sup> The results of angioplasty have been disappointing.<sup>7-10</sup> Angioplasty of vein grafts is associated with increased rates of procedural complications and restenosis.<sup>11-12</sup> Stent implantation has been proved to be superior to balloon angioplasty alone.<sup>13-14</sup> Yet the recurrence rate after stenting still reaches 50%.<sup>15</sup> Treatment of in-stent restenosis is limited by repeat recurrence rates of 40–60% regardless of the angioplasty modality used.<sup>16-17</sup>

Vascular brachytherapy (VBT), using either  $\gamma$  or  $\beta$  radiation sources, has been associated with a very significant impact on the restenosis process. Five randomised trials have shown that both  $\gamma$  and  $\beta$  VBT are associated with a significant decrease in angiographic restenosis and need for target vessel revascularisation in in-stent restenotic lesions.<sup>18-22</sup> For de novo lesions, results have been less conclusive. Excellent results were obtained in one uncontrolled dose finding trial<sup>23</sup> when a high dose of  $\beta$  brachytherapy was given following balloon angioplasty without stent implantation, but a larger randomised controlled evaluation<sup>24</sup> suggested that the angiographic and clinical benefit of VBT was only small following balloon angioplasty alone and was non-existent when a stent was implanted at the time of VBT.

For the treatment of SVG lesions only very limited data exist. In the majority of randomised trials SVG lesions were excluded. In both the  $\gamma$ -WRIST (Washington radiation for in-stent restenosis trial) and SCRIPPS-I (Scripps coronary radiation to inhibit proliferation poststenting) trials the prevalence of interventions in SVG was 23%. No subgroup analyses have been performed. The only randomised trial on VBT in SVG used  $\gamma$  radiation for the treatment of in-stent restenosis and showed reduction of restenosis rate and need for repeat revascularisation of 50%.<sup>17</sup>

To investigate the potential benefit of  $\beta$  radiation in SVG, we conducted a retrospective subgroup analysis from clinical data that had been collected in the European registry of intraluminal coronary  $\beta$  brachytherapy (RENO). Since follow up angiography was not mandatory in this registry, quantitative angiographic analysis was performed retrospectively from available data.

**Abbreviations:** CABG, coronary artery bypass grafting;  $\gamma$ -WRIST, Washington radiation for in-stent restenosis trial; MACE, major adverse cardiac event; RENO, European registry of intraluminal coronary  $\beta$  brachytherapy; SCRIPPS-I, Scripps coronary radiation to inhibit proliferation poststenting; SVG, saphenous vein bypass grafts; VBT, vascular brachytherapy

## PATIENTS AND METHODS

### Population and data collection

Sixty seven of 1098 (6.1%) consecutive patients in the RENO trial underwent angioplasty and VBT of SVG lesions. Data were prospectively collected. All serious adverse events were requested to be reported by fax within 48 hours of their occurrence. Centres obtained institutional review board or ethics committee approval, as well as signed informed consent from the patients. Baseline clinical characteristics, indication for VBT, type of percutaneous intervention and VBT performed, in-hospital events, and six month follow up data were recorded. Index and follow up coronary angiograms, if available, were collected, and quantitative coronary angiography analysis was performed using a validated system (CAAS II, Pie Medical, Maastricht, Netherlands).

### Definitions

Technical success was considered to have been achieved when at least 90% of the planned dose of radiation had been delivered to the target coronary segment and the final residual stenosis was no greater than 50%. Acute myocardial infarction was defined as an increase in plasma creatine kinase concentration above twice the upper limit of normal, new Q waves on the ECG, or both. The infarction was considered to be related to the VBT procedure if it occurred in the territory of a treated coronary artery or if its location could not be determined. Deaths were classified as cardiac or non-cardiac, and cardiac death was further defined as sudden (within 24 hours of acute symptoms onset) or non-sudden. Deaths of undetermined cause were deemed to have been cardiac.

A major adverse cardiac event (MACE) was considered to have occurred if one or several of the following were documented: death, myocardial infarction, or target vessel revascularisation. Angiographic restenosis was considered present when a 50% or greater diameter stenosis in the target vessel was present.

### VBT procedure

A femoral access was used in all cases. The angioplasty procedure was performed according to the operator's discretion. A satisfactory initial acute result was a prerequisite for subsequent VBT, but stents could be implanted either before or after irradiation. VBT was carried out using a monorail-type 5 French delivery catheter (Novoste, Norcross, Georgia, USA) to deliver hydraulically a source train of Sr/Y<sup>90</sup> seeds 30, 40 or 60 mm in length. The recommended dose, prescribed at 2 mm from the longitudinal axis of the source train, varied between 16.1–23.0 Gy for patients without, and between 18.4–25.3 Gy for patients with, a previously implanted stent according to the reference diameter. The nominal diameter of the largest angioplasty balloon used before VBT was taken as the reference diameter. The 40 mm and 60 mm source trains became available only during patient recruitment, and several centres occasionally resorted to a "pullback" manoeuvre (positioning of the delivery catheter twice over adjacent segments of the injured segment of the target vessel). Following the procedure, patients were treated with aspirin together with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily. On the basis of the available information at the time of protocol design, a minimum of 90 days of combined antiplatelet treatment was recommended, but each investigator was free to prolong this if it was thought necessary.

### Quantitative coronary angiography

Quantitative coronary analysis was performed off line using the CAAS II system. Measurements were carried out before the intervention, after the very last step of the index procedure, and at follow up. The minimal lumen diameter was determined by edge detection and the reference diameter was automatically calculated by the interpolated method. The per-

**Table 1** Baseline clinical and angiographic characteristics

Number of patients	67
Number of lesions	68
Mean (SD) age (years)	66 (10)
Male sex	58 (86.6%)
Diabetes	21 (31.3%)
Hypertension	45 (67.2%)
Hyperlipidaemia	53 (79.1%)
Smoking	7 (10.4%)
Unstable angina	28 (41.8%)
Prior acute myocardial infarction	21 (31.3%)
Type of lesion*	
In-stent restenosis	53 (77.9%)
De novo stenosis	13 (19.1%)
Non-stented restenosis	2 (3.0%)
Target lesion location*	
SVG on the obtuse marginal branch	37 (54.4%)
SVG on the left anterior descending coronary artery	14 (20.6%)
SVG on the right coronary artery	11 (16.2%)
SVG on the diagonal branch	6 (8.8%)
Lesion position in SVG*	
Body	41 (60.3%)
Ostium	21 (30.9%)
Distal anastomosis	6 (8.8%)

\*Results per lesion. SVG, saphenous vein graft.

centage diameter stenosis was calculated from the minimal lumen diameter and the reference diameter.

### Statistical methods

Calculations were performed using a dedicated software package (SPSS 10.0.7, SPSS Inc, Chicago, Illinois, USA). Categorical data are presented as absolute and relative frequencies. For continuous variables, arithmetic means (SD) are given as summary measures. Continuous variables were compared using unpaired Student's *t* test. A probability value of  $p < 0.05$  was considered significant.

## RESULTS

### Baseline demographic and angiographic characteristics

Table 1 shows the baseline characteristics. Most patients were male and exhibited a typical prevalence of cardiovascular risk factors. Of note, the percentage of patients with unstable angina pectoris was comparably high. The most frequent indication for VBT was in-stent restenosis. Roughly half of the procedures were performed in the SVG supplying the obtuse marginal branch of the left circumflex coronary artery. Most of the lesions were confined to the graft's body but ostial interventions were also very common.

### Angioplasty and VBT

Table 2 lists the procedure related parameters. Debulking techniques before balloon angioplasty and VBT were not used at all. The cutting balloon was used in only a minority of cases. Most of the procedures did not include the implantation of a new stent. Because of insufficient back up of the guiding catheter preventing passage of the radiation delivery catheter the overall primary success rate was only 91.2%.

### Quantitative coronary angiography

Table 3 gives the quantitative coronary angiography data. Follow up angiography was performed after a mean (SD) of 6.9 (2.0) months. Of note, the lesion length was above average. Because of the large reference lumen diameter, acute lumen gain approximated 3 mm. A significantly larger mean acute gain in luminal diameter was achieved when de novo lesions were treated. Because of an additional trend for lower late loss, the minimum lumen diameter at follow up was significantly higher in de novo lesions than in in-stent restenosis.

### Clinical follow up

In-hospital and six month clinical follow up data were obtained for all patients after a mean (SD) of 6.3 (2.4) months. During the hospital stay none of the patients suffered an acute myocardial infarction or cardiac death. One of the patients required catheter based reintervention because of a thrombotic reocclusion of a severely degenerated SVG, which had been treated with stent implantation for a de novo lesion. Clopidogrel had not been discontinued. Two patients died of non-cardiac causes (pneumonia of intracerebral bleeding). The overall in-hospital MACE rate was 4.5%.

At six months' follow up one of the patients had a non-Q wave acute myocardial infarction. Another patient had a Q wave acute myocardial infarction requiring reintervention and leading to cardiac death. Cardiac death occurred in another two patients. One was sudden in nature and was caused by ventricular fibrillation during a dental procedure. The other one was caused by protracted intrathoracic bleeding after semi-elective CABG. Five patients died of non-cardiac causes (two pneumonia, one adult respiratory distress syndrome, one septic shock, and one intestinal ischaemia). The angiographic restenosis rate was 18.6% and the target vessel revascularisation rate was 16.4% (13.4% percutaneous transluminal coronary angioplasty, 3.0% CABG). The overall MACE rate was 26.9%.

### DISCUSSION

Recurrent myocardial ischaemia after CABG is a common clinical problem. Angiographic studies have found that within 10 years after the operation, half of all vein grafts are totally occluded or have severe atherosclerotic disease.<sup>1-4</sup> Repeated bypass surgery is more technically challenging than a first operation, is associated with higher morbidity and mortality, and provides less symptomatic relief.<sup>5-6</sup> Angioplasty is therefore often attempted. However, the results of balloon angioplasty in SVG are less favourable than those in native vessels regarding complication and restenosis rates.<sup>7-8 11 12</sup> Stent implantation has been shown to be superior to balloon angioplasty in observational as well as in randomised trials.<sup>13 14</sup> Despite these encouraging findings the absolute restenosis rate after PTCA of SVG is still high and subsequent clinical sequelae are meaningful.<sup>15</sup> Interventional treatment of in-stent restenotic lesions is associated with a repeat recurrence rate of 50% regardless of the technique performed.<sup>16 17</sup> Thus, it seemed reasonable to attempt to reduce the incidence of restenosis, either prophylactically by combin-

ing the primary intervention of a de novo lesion with VBT or as an adjunctive treatment modality.

While VBT in native coronary arteries is now very solidly documented in five randomised trials,<sup>18-22</sup> only one randomised trial for the treatment of SVG disease exists.<sup>17</sup> Gamma radiation was applied to in-stent restenotic lesions exclusively. A very prominent reduction of restenosis rate (iridium-192 15%, placebo 43%,  $p = 0.004$ ) and of the composite end point of death, Q wave myocardial infarction, and target vessel revascularisation (iridium-192 32%, placebo 63%, odds ratio 0.27, 95% confidence interval 0.13 to 0.57,  $p < 0.001$ ) has been shown. Considering the complexity of the treated lesions, it was concluded that VBT is of special value for patient subsets at high risk for recurrent events. The present data from the RENO registry reflect a subgroup of patients having undergone  $\beta$  irradiation in SVG during routine clinical practice. The high rates of six month clinical and angiographic follow up that were achieved (100% and 91%, respectively) give particular strength to the observations that can be made.

Performing VBT in SVG lesions is feasible and safe. Nevertheless, the primary success rate was comparably low. This was because of insufficient back up of the guiding catheter to allow passage of the relatively stiff 5 French radiation delivery catheter to the target lesion. More flexible delivery catheters with a lower profile may be preferable for VBT in SVG.

In-hospital complications were infrequent (4.5%), and comparable with other series of coronary interventions in SVG.<sup>11 12</sup> This seems to be favourable, since interventions in SVG lesions usually are associated with the highest risk and the prevalence of patients with unstable angina and ostial lesion location, as well as lesion length, was above average.

The six month MACE rate of 26.7% observed in the present registry compares with those reported in the radiotherapy arm of the available trials,<sup>17-22</sup> where the MACE rate varied between 18-29% for patients treated for in-stent restenosis and between 14-19% for de novo lesions. Of note, 7.5% of the overall MACE rate was caused by non-cardiac deaths. These deaths were not procedure related and reflect the high level of morbidity of the study population. Yet, in light of the limited sample size, the number should be regarded with caution. The need for target vessel revascularisation was 16.4% in this registry, while it was 11-34% in previously conducted studies. This seems to be especially favourable, for several reasons. Firstly, the absolute rate of reinterventions is at the lower end of the results reported in previous trials. Secondly, the

**Table 3** Results of quantitative coronary angiography

	Overall (n=67)	In-stent restenosis (n=46)	De novo/restenosis (n=21)	p Value
Lesion length (mm)	23.56 (20.38)	26.13 (22.93)	17.94 (11.77)	0.058
Pre-intervention				
Reference lumen diameter (mm)	4.19 (0.52)	4.22 (0.52)	4.15 (0.54)	0.626
Minimum lumen diameter (mm)	0.73 (0.62)	0.75 (0.61)	0.69 (0.67)	0.738
Diameter stenosis (%)	82 (15)	82 (15)	84 (15)	0.617
Postintervention				
Reference lumen diameter (mm)	4.21 (0.53)	4.23 (0.53)	4.15 (0.54)	0.560
Minimum lumen diameter (mm)	3.77 (0.69)	3.64 (0.68)	4.05 (0.65)	0.023
Diameter stenosis (%)	11 (11)	14 (11)	3 (7)	<0.001
At follow up				
Reference lumen diameter (mm)	4.20 (0.53)	4.23 (0.55)	4.13 (0.51)	0.510
Minimum lumen diameter (mm)	2.94 (1.50)	2.69 (1.42)	3.53 (1.56)	0.049
Diameter stenosis (%)	31 (34)	37 (32)	18 (34)	0.047
Binary restenosis (%)	18.6	21.4	11.8	0.388
Change in minimum lumen diameter				
Acute gain (mm)	3.02 (0.88)	2.87 (0.90)	3.35 (0.77)	0.038
Late loss (mm)	0.86 (1.25)	1.02 (1.27)	0.48 (1.14)	0.128
Net gain (mm)	2.15 (1.54)	1.95 (1.55)	2.64 (1.45)	0.094

Data are mean (SD).

incidence of reintervention in a high risk patient subset reported in this trial is essentially the same as in a population at average risk. It should also be stressed that several exclusion criteria often used in randomised trials did not apply in this registry. Although the protocol initially discouraged the irradiation of lesions longer than 30 mm, this was nevertheless done for 21 lesions (30.9%) and a pullback manoeuvre was used for 17 (25.0%).

Several points demand special attention. Usually, the implantation of a new stent in conjunction with VBT is associated with an increased risk for late thrombosis and eventual late thrombotic occlusion, as well as an increased likelihood of target vessel revascularisation caused by geographic miss and consecutive edge effect.<sup>20-24-26</sup> In the population studied, no such observation could be made. De novo lesions, although of smaller length, exhibited a larger acute gain, a smaller late loss, and neither total occlusion nor an edge effect. Thus, stent implantation for de novo lesions in SVG may not necessarily be attributable to a higher rate of repeat reinterventions or MACE. Yet, to draw any valid conclusions, larger sample sizes are imperative.

### Limitations

Although the results of the present series are very encouraging, they suffer from the limitations of all registries. They cannot be seen as direct evidence of the efficacy of VBT, especially in a heterogeneous population. The sample size was small, limiting conclusions concerning clinical end points.

Angiographic follow up was not mandatory, resulting in an incomplete data set. Nevertheless, the actual angiographic follow up rate was high and not only driven by clinical need but more often based on a compassionate manner. Quantitative coronary angiography was performed retrospectively. Thus, angiography was performed in a non-standardised manner resulting in potential errors in determining true vessel dimensions. Since SVG, in contrast to native coronary arteries, are of greater diameter and do not pose the problem of overlay with other vessels, sources of error are likely to be acceptable.

It is important to emphasise limitations resulting from the open nature of this trial, since patients and operators were not blinded to the treatment. Thus, the possibility of bias cannot be excluded despite the prospective design of the registry.

### Conclusions

Adjunct VBT with  $\beta$  radiation for de novo and in-stent restenotic lesions in SVG is feasible and can be safely performed. At six months' follow up, the restenosis rate compares very favourably with previously reported data acquired in populations with a much lower likelihood of recurrence, and MACE rates are similar to those obtained in the VBT arms of published randomised controlled trials. Thus,  $\beta$  VBT might be of special value for high risk patient subsets. It would be desirable to confirm the results in a randomised controlled trial.

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## IMAGES IN CARDIOLOGY.....

### Left ventricular microaneurysms as a cause of apparently idiopathic ventricular fibrillation

A 36 year old woman had been involved in a traffic accident because of syncope. A paramedic witnessed the accident by chance. He diagnosed cardiac arrest and started cardiopulmonary resuscitation. ECG recorded by an automatic external defibrillator revealed ventricular fibrillation. Regular sinus rhythm was successfully restored by a single 200 Joule direct current shock (below, ECG at admission). The patient recovered well within one day without any neurological sequelae. She reported a five year history of recurrent episodes of palpitations without previous syncope. ECG evaluation performed by the patients' general practitioner a few years ago revealed multiple ventricular premature beats. No further cardiac evaluation had been performed in the past.

Coronary angiography revealed normal coronary arteries. Right anterior oblique angiographic projection of the left ventricle (right) revealed four left ventricular microaneurysms. The global left ventricular ejection fraction was 72%. Two dimensional echocardiography, performed by an

experienced operator, failed to show abnormalities of cardiac morphology. Implantation of a defibrillator was performed six days following the successful resuscitation.

Severe ventricular arrhythmias may occur in patients with apparently normal hearts and may be associated with inflammatory left ventricular aneurysms of small dimension. Inflammatory left ventricular microaneurysms are often of viral origin (caused by previous myocarditis) and this finding is a consistent cause of the apparently "idiopathic" ventricular fibrillation in this case.

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