The pattern of restenosis and vascular remodelling after cold-end radioactive stent implantation

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**Background** Edge restenosis is a major problem after radioactive stenting. The cold-end stent has a radioactive mid-segment (15.9 mm) and non-radioactive proximal and distal 5.7 mm segments. Conceptually this may negate the impact of negative vascular remodelling at the edge of the radiation.

**Method and Results** ECG-gated intravascular ultrasound with three-dimensional reconstruction was performed post-stent implantation and at the 6-month follow-up to assess restenosis within the margins of the stent and at the stent edges in 16 patients. Angiographic restenosis was witnessed in four patients, all in the proximal in-stent position. By intravascular ultrasound in-stent neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Echolucent tissue, dubbed the ‘black hole’ was seen as a significant component of neointimal hyperplasia in six out of the eight cases of restenosis. Neointimal hyperplasia was inhibited in the area of radiation: Δ neointimal hyperplasia=3.72 mm³ (8.6%); in-stent at the edges of radiation proximally and distally Δ neointimal hyperplasia was 7.9 mm³ (19.0%) and 11.4 mm³ (25.6%), respectively (P=0.017). At the stent edges there was no significant change in lumen volume.

**Conclusions** Cold-end stenting results in increased neointimal hyperplasia in in-stent non-radioactive segments.


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**Key Words:** Stents, remodelling, radioisotopes, angioplasty, ultrasonics.

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**Introduction**

Conventional stenting has eliminated recoil and negative remodelling of the restenotic process. However, this has been at the cost of exacerbating neointimal proliferation secondary to chronic vessel wall irritation, leading to in-stent restenosis[1,2].

Intracoronary radiation has been developed in an attempt to decrease restenosis after balloon angioplasty and stent implantation. Studies recently performed in humans demonstrated a dose-dependent inhibition of neointimal hyperplasia at the 6-month follow-up in stents with activity levels >3 µCi[3,4]. However, a significant increase in neointimal hyperplasia was noted at the extremes of the stent and at the edges. Edge restenosis was mainly due to an increase in plaque and to a lesser extent, remodelling of the native vessel wall[4,5]. A fall-off in radiation in areas receiving vascular injury was proposed as a possible stimulatory mechanism. In order to minimize the effect of vascular remodelling on stent-edge restenosis, the stent design was modified. The ‘cold-end’ stent (Isostent® Inc., San Carlos, CA, U.S.A.) was rendered radioactive in its mid-portion (15.9 mm in length); the edges (5.7 mm each) were non-radioactive (Fig. 1).

We aimed to analyse tissue growth within the stent and at its edges and to define the segments that had the greatest propensity to restenosis after the implantation of a cold-end stent.
Methods

Patient selection

We analysed neointimal hyperplasia and vascular remodelling in 16 patients who had completed a 6-month angiographic follow-up with intravascular ultrasound analysis. All patients had single native vessel coronary artery disease, normal left ventricular function and objective evidence of ischaemia.

Implantation technique

Pre-dilation of the lesion was performed where necessary followed by stent implantation. High-pressure balloon inflation to ensure good strut apposition to the vessel wall was then performed at the operator’s discretion. At this time we used a shorter balloon to ensure that the edges of the balloon did not extend beyond the limits of the stent. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10 000 international units of heparin at the initiation of the procedure and the activated clotting time was maintained at >300 s. All patients received aspirin 80 mg daily indefinitely and clopidogrel 75 mg daily for 6 months.

Radioactive stent

The stent was 27.3 mm in length and available in diameters of 3.0 and 3.5 mm. It was made radioactive in its central portion by phosphorus-32 (32P)[3]. The 5.7 mm edges were shielded from radiation. The initial activity of the stents was measured and thereafter it was calculated at what date the activity had decreased to 3.0–12.0 µCi, suitable for implantation.

Intravascular ultrasound image acquisition analysis

After the final balloon inflation and administration of intracoronary nitrates, ECG-gated intravascular ultrasound pullback was performed. This was repeated at the 6 month follow-up. The segment was subjected to three-dimensional reconstruction and examined with a mechanical intravascular ultrasound system (Clearview, CardioVascular Imaging System, Sunnyvale, CA, U.S.A.) with a sheath-based intravascular ultrasound catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. The intravascular ultrasound transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor[6]. Intravascular ultrasound images were acquired, coinciding with the peak of the R wave, which eliminates the artefacts caused by the movement of the heart during the cardiac cycle. After each image acquisition, the transducer was withdrawn 0.2 mm to acquire the next image coincident with the R-wave. By definition, this permits acquisition of five slices per mm, enabling the operator to easily define the stent margins. By increasing the frequency of sampling this approach may also decrease error due to regression to the mean created by the use of greater step sizes and non-ECG-gating[7,8].

ECG-gated image acquisition and digitization was performed using a workstation designed for three-dimensional reconstruction of echocardiographic images[6] (EchoScan, Tomtec, Munich, Germany). A Microsoft Windows-based contour detection program, developed at the Thoraxcenter, was used for automated three-dimensional analysis of up to 200 intravascular ultrasound images[9]. This program constructs two longitudinal sections and identifies the contours corresponding to the lumen–intima and media–adventitia boundaries, using a minimum-cost based software algorithm. The feasibility, reproducibility and the inter- and intra-observer variability of this system have been previously described in clinical protocols[5,9].

Quantitative intravascular ultrasound analysis

At the stent edges, the area encompassed by the lumen–intima and media–adventitia boundaries defined the luminal and the total vessel volumes, respectively. The difference between luminal and total vessel volumes defined the plaque volume. Within the boundaries of the stent total vessel volume, stent volume, neointimal hyperplasia, and lumen volumes were obtained. The
neointimal hyperplasia presented was a value measured at follow-up (stent volume-lumen volume).

The assessment of total vessel volume in stented patients has previously been reported\(^5,10\). In our study the delineation of the total vessel volume boundary was possible in all stented patients. When the total vessel volume boundary was not visible in a single cross-sectional view, the computer extrapolated it from the contours of the immediately previous and following cross-sections. In addition, the use of three-dimensional reconstruction with multiple longitudinal views, facilitates the visualization of vessel structures outside the stent.

**Definitions and segments of analysis**

Stent edges were defined as those volumes axially 5 mm proximal and distal to the final stent strut. In addition, segments in-stent proximally and distally were analysed separately to assess neointimal hyperplasia in areas which were subject to injury and received stent implantation. Effectively, these were segments which received a fall-off in radiation. Finally the in-stent radioactive segment was analysed (see Fig. 1). To facilitate comparison between the non-radioactive in-stent segments (5·7 mm) and the central radioactive segment (15·9 mm), lengths were normalized to a standard length (5 mm) and appropriate comparisons made. Restenosis was defined as an angiographic restenosis >50% at 6-month follow-up, by off-line quantitative coronary angiography.

**Statistical analysis**

Quantitative data are presented as mean ± standard deviation. Volumetric data derived from the three-dimensional reconstruction of the intravascular ultrasound image were compared immediately after treatment and at follow-up using the two-tailed paired Student’s t-test. ANOVA was used to compare multiple variables. A value of \(P<0·05\) was considered statistically significant.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study and all patients provided written informed consent before the procedure.

**Results**

Baseline clinical and procedural characteristics are described in Tables 1 and 2. Table 3 describes quantitative coronary angiography data pre- and post-intervention and at the 6-month follow-up.

**In-stent radioactive segment**

Neointimal hyperplasia measured within the margins of the stent is presented in Fig. 2. Intra-stent neointimal hyperplasia was significantly decreased in the radioactive mid-segment of the stent: \(3·72 ± 3·3\) mm\(^3\) (8·6%) compared with the proximal: \(7·90 ± 7·2\) mm\(^3\) (19·0%) and distal: \(11·42 ± 10·5\) mm\(^3\) (25·6%) in-stent segments. Over the entire stent length there was a 30·48 mm\(^3\) (14%) increase in neointimal hyperplasia. No evidence of remodelling was seen behind the stent with the total vessel volume remaining unchanged.

**In-stent non-radioactive segment**

Significant neointimal in-growth was noted distally and proximally from 2–3 mm within the radioactive segment and extended on average to the extremities (non-radioactive) of the stent (see Fig. 3). Four individuals experienced angiographic restenosis in the proximal

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**Table 1 Clinical characteristics**

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<th>Variable</th>
<th>Pre</th>
<th>Post</th>
<th>FU</th>
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<tr>
<td>Age (mean)</td>
<td>52</td>
<td>44</td>
<td>78</td>
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<tr>
<td>Male (%)</td>
<td>69</td>
<td>69</td>
<td>75</td>
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<td>Prior MI (%)</td>
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<tr>
<td>Smoking (%)</td>
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<td>Hypercholesterolaemia (%)</td>
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<td>Family history (%)</td>
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<tr>
<td>Diabetes (%)</td>
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**Table 2 Procedural characteristics**

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<td>Vessel</td>
<td>LAD</td>
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<tr>
<td></td>
<td>LCs</td>
<td>7</td>
<td>7</td>
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<tr>
<td></td>
<td>RCA</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Lesion length (mm)</td>
<td>11±2</td>
<td>4±5</td>
<td>4±5</td>
</tr>
<tr>
<td>Balloon length-post (mm)</td>
<td>15±6</td>
<td>5±7</td>
<td>5±7</td>
</tr>
<tr>
<td>Final balloon size (mm)</td>
<td>3±9</td>
<td>0±5</td>
<td>0±5</td>
</tr>
<tr>
<td>Max inflation pressure(^1) (atms)</td>
<td>10±4</td>
<td>0±4</td>
<td>0±4</td>
</tr>
<tr>
<td>Max inflation pressure(^2) (atms)</td>
<td>16±2</td>
<td>2±2</td>
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<tr>
<td>Balloon-to-artery ratio</td>
<td>1±1</td>
<td>2±2</td>
<td>2±2</td>
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**Table 3 Angiographic data**

<table>
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<th>Post</th>
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<tr>
<td>MLD</td>
<td>0·98±0·40</td>
<td>2·26±0·40</td>
<td>1·67±0·48</td>
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<td>DS</td>
<td>67±14</td>
<td>26±8</td>
<td>42±13</td>
</tr>
<tr>
<td>RD</td>
<td>2·97±0·46</td>
<td>3·06±0·41</td>
<td>2·82±0·43</td>
</tr>
<tr>
<td>Acute gain</td>
<td>1·28±0·46</td>
<td>1·28±0·46</td>
<td>1·28±0·46</td>
</tr>
<tr>
<td>Late loss</td>
<td>0·59±0·49</td>
<td>0·59±0·49</td>
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<tr>
<td>Late loss index</td>
<td>0·57±0·56</td>
<td>0·57±0·56</td>
<td>0·57±0·56</td>
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</table>

FU=6-month follow-up.
MLD=minimum lumen diameter; DS=diameter stenosis; RD=reference diameter.
portion of the stent. However, the greatest mean volume of tissue growth as quantified by intravascular ultrasound was seen in the distal stent. Neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Tissue growth in-stent was due to a combination of conventional neointimal hyperplasia and echolucent, hypodense material, described by this group as the ‘black hole’ (P. W. Serruys, personal communication, Rotterdam, 1999). This was witnessed (Fig. 4) in the non-radioactive proximal and distal in-stent segments in six out of the eight patients.

Figure 2 Neointimal hyperplasia (mm³) in the three in-stent segments. Each segment is standardized to a 5 mm length for comparison.

ANOVA, p = 0.017

Figure 3 Graph showing neointimal hyperplasia (% increase) over the length of the stent and edges. Note significant hyperplasia proximally and distally in-stent and the relative sparing of the radioactive mid-segment of the stent. Note also that significant in-growth begins within the radioactive segment of the stent and extends to the non-radioactive proximal and distal extremities of the stent.

Total vessel volumes

No significant change in total vessel volumes or plaque behind the stent was seen between post-procedure and follow-up. No echolucent tissue was seen behind the stent.

Stent edge

Late lumen loss was seen at the stent edge without evidence of restenosis. On average, there was evidence of a decrease in total vessel volume, with little change in plaque as a cause of late lumen loss.

Stent activity

Mean stent activity at implantation was 6.9 ± 1.9 μCi.

Discussion

Dose-finding studies in humans have shown that in-stent neointimal hyperplasia is decreased in a dose-dependent manner after the implantation of stents with activity levels >3.0 μCi[3,4]. Unfortunately, stent edge restenosis was a side effect of this treatment modality at these activity levels. Because the stent edge is systematically
damaged by barotrauma at the time of balloon expansion, a situation of geographical miss\(^{[11]}\), in which the damaged edges receive low dose radiation, is germane to radioactive stenting in the absence of appropriately shaped balloons. Previously we have argued: ‘If the candy wrapper (bilateral edge restenosis) were purely the result of negative remodeling induced by low-dose radiation in an injured area, then the lengthening of the stent by a non-radioactive, cold-end would be a logical solution to prevent remodeling at the extremities. If plaque constitutes a large percentage of the healing process manifested by the candy wrapper then cold-end stent implantation is unlikely to work. Similarly neointimal proliferation may occur at the edges of the radiation within stent using this treatment modality\(^{[12]}\). This prediction appears to have materialized in the current study, with migration of the restenotic edge from outside the stent to within the stent at the edges of radiation.

**Neointimal hyperplasia**

Neointimal hyperplasia in the true radioactive segment was suppressed at the 6-month follow-up to a degree similar to that noted in the \(^{32}\)P radioactive stent dose-finding trial previously reported by this group (mean neointimal hyperplasia = 17.67 mm\(^2\) (13-94\%)), using a 15 mm stent\(^{[5]}\). Regrowth of tissue starting 1–2 mm within the radioactive extremes and extending out of the stent was noted in the \(^{32}\)P radioactive stent dose finding trial, translating to significant stent-edge hyperplasia proximally. In the cold-end stent, neointimal hyperplasia was noted in the final millimeters of radiation and extended bilaterally. In the latter study, this left the true stent edges relatively, although not completely, spared as there remained evidence of tissue growth in three individuals, which started within the radioactive portion and continued to the true vessel lumen. No angiographic restenosis occurred in these three however. Again, we must assume that the position of such restenosis is caused by geographical miss. Why some individuals are affected and others not is unclear, but may be explained by an idiosyncratic individual response to healing, dose heterogeneity along the length of the stent, tissue type behind the stent, plaque burden and even strut apposition to the vessel wall.

**Echolucent tissue**

In nearly 50\% of subjects, echolucent tissue was present within the stent at the distal or proximal (in-stent) edge of radiation and constituted on average 50\% of neointimal ingrowth in areas of restenosis. These echolucent lesions had the following characteristics: a homogeneous black appearance without backscatter. Images with ring-down or other artefacts were excluded and no attenuation behind intraluminal echodense structures was seen. Exclusion of other causes of relative echolucency such as contrast\(^{[13]}\), thrombus\(^{[14]}\) or a lipid lake\(^{[15]}\) was performed. Lesions were discrete and readily distinguishable from conventional neointimal hyperplasia. After radioactive stenting, all appeared to be juxtaposed to stent struts.

We have performed atherectomy on four such lesions detected at the 6-month follow-up after radioactive stenting and found that they contain a hypocellular matrix with areas of proteoglycan, similar to that seen in the animal model\(^{[16,17]}\). The mixture of neointimal hyperplasia and proteoglycan, which has a high water content, may explain the echolucent tissue adjacent to the stent struts noted in Fig. 5. Further pathological
assessment is required before definitive comment can be made on this interesting observation. Equally, the long-term incidence of restenosis from such lesions is yet to be determined.

**Edge remodelling**

This was similar to that seen after non-radioactive stenting, whereby non-restenotic late lumen loss was due to negative remodelling\(^5\,^1^8\).

*Implications for the future: dealing with the edge effect*

If the edge effect is the result of balloon-induced trauma and low dose radiation then limiting the trauma to outside the stent and expanding the irradiated area beyond the injured area should be attempted. For radioactive stents, conceivably the most practical approach may be to extend the area of irradiation beyond the injured area using a ‘hot-end stent’. This involves literally concentrating the greatest activity of the stent at

*Figure 5* Photomicrographs (a) and (b) show neointima consisting of arborizing smooth muscle cells in a proteoglycan matrix. H&E stain; bars=50 μm.
the stent edges; such stents are already undergoing multicentre trials. A further therapeutic option is that of hybrid treatment with radioactive stent implantation followed by catheter-based therapy localized to the stent edges only.

**Conclusion**

Cold-end stent implantation, a strategy devised to prevent edge restenosis after radioactive stenting results in migration of the restenotic edge from outside the stent to within the stent at the edges of radiation. This adds credence to the hypothesis that injury and low-dose radiation stimulate neointimal hyperplasia.[19]

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**References**


