Initial observation regarding changes in vessel dimensions after balloon angioplasty and stenting followed by catheter-based β-radiation

Is stenting necessary in the setting of catheter-based radiotherapy?

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Aims We sought to compare the effect of intracoronary β-radiation on the vessel dimensions in de novo lesions using three-dimensional intravascular ultrasound quantification after balloon angioplasty and stenting.

Methods and Results Forty patients (44 vessels; 28 balloon angioplasty and 16 stenting) treated with catheter-based β-radiation and 18 non-irradiated control patients (18 vessels; 10 balloon angioplasty and 8 stenting) were investigated by means of three-dimensional volumetric intravascular ultrasound analysis post-procedure and at 6–8 months follow-up. Total vessel (EEM) volume enlarged after both balloon angioplasty and stenting (+37 mm³ vs +42 mm³, P=ns), but vessel wall volume (plaque plus media) also increased similarly (+33 mm³ vs +49 mm³, P=ns) in the irradiated patients. Lumen volume remained unchanged in both groups (+3 mm³ vs −7 mm³, P=ns). In the stent-covered segments, neointima at follow-up was significantly smaller in the irradiated group than the control group (8 mm³ vs 27 mm³, P=0.001, respectively), but the total amount of tissue growth was similar in both groups (33 mm³ vs 29 mm³, P=ns).

Conclusions Intracoronary β-radiation induces vessel enlargement after balloon angioplasty and/or stenting, accommodating tissue growth. Additional stenting may not play an important role in the prevention of constrictive remodelling in the setting of catheter-based intracoronary β-radiotherapy.


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Introduction

The safety and feasibility of catheter-based intra-coronary γ- or β-irradiation has been established in clinical trials[1–3]. Randomized studies have demonstrated the reduction of restenosis in patients with restenotic lesions[4,5]. Recently, β-irradiation was shown to inhibit the recurrence of restenosis (⁶[Popma ACCIS 2000 presentation, START trial]). A non-randomized study using β-radiation to treat de novo coronary lesions has also shown promising results in the reduction of restenosis rate after balloon angioplasty[⁷]. It is of note that European experiences have been more oriented to β-radiation for de novo lesions, whereas in the U.S., most efforts have been focusing on the γ-radiation for in-stent restenosis[⁸].

Restenosis after angioplasty is caused by two components: vessel remodelling and neointimal formation. Data from experimental models have demonstrated the...
inhibition of neointimal formation and of constrictive negative remodelling after intracoronary radiation[9–12]. Recently, these findings were confirmed in human coronary arteries using sophisticated three-dimensional volumetric intravascular ultrasound[13]. In this era of stent implantation, the effect of brachytherapy in stented arteries deserves careful evaluation, and one small study has suggested that an increase in plaque volume occurred after brachytherapy mainly outside the stent[14].

The aim of the present study was to investigate the effect of intracoronary β-radiation on the vessel dimensions of de novo lesions after balloon angioplasty and stenting using three-dimensional intravascular ultrasound quantification.

**Methods**

**Patients**

From April 1997 to May 1999, 64 de novo lesions (57 patients) were consecutively treated with catheter-based intracoronary β-radiation using the Beta-Cath System® (Novoste Corp., Norcross, GA). Intravascular ultrasound analyses of 10 vessels (7 patients) were not included in this study due to the implantation of multiple overlapping stents outside the irradiated segments because of the inability to define the region of interest. An additional 10 vessels (10 patients) were not included because three-dimensional-intravascular ultrasound analysis was not performed either post-procedure or at follow-up (3 patients had severe restenosis, 1 patient met intravascular ultrasound crossing failure at baseline, 3 presented thrombotic occlusion, and 3 other patients refused follow-up angiograms). The control group consists of 18 patients successfully treated with conventional balloon angioplasty (n=10) or single stent implantation (n=8) during the same period. In these patients, the radiation delivery catheter was also introduced in the target coronary arteries, but a dummy source was used instead of a radioactive source as placebo groups for brachytherapy trials.

The study population consists of 40 irradiated patients (44 vessels; 28 treated with balloon angioplasty and 16 treated with stenting) and 18 non-irradiated placebo patients (18 vessels). Patients presented with angina pectoris or positive stress testing. Patients with myocardial infarction within 72 h prior to treatment or left ventricular ejection fraction <30% were not included in this study. Angiographic inclusion criteria consisted of a reference vessel diameter >2.5 mm and <4.0 mm and a lesion length <20 mm. Only slotted tube stents were used for this study.

The Medical Ethics Committee of the University Hospital Rotterdam Dijkzigt approved the protocol of intracoronary radiation. All patients gave written informed consent.

**Radiation system**

The source train of the Beta-Cath® System consists of a series of 12 independent cylindrical seeds, which contain pure β-emitting ⁹⁰Sr/⁸⁹Y, and is bordered by two gold markers (30 mm total length of radioactive seeds). The profile of the catheter is 5 French and the source train is not centered. The radiation sources remain at the treatment site for approximately 2–4 min to deliver a predetermined dose at 2 mm from the centreline of the axis of the source train. Prescribed radiation doses were 12Gy (8 vessels), 14Gy (12 vessels), 16Gy (9 vessels), and 18Gy (15 vessels).

**Procedure**

All patients received aspirin (250 mg·day⁻¹) and heparin IV (10 000 IU) during the procedure and additional heparin was given to maintain the activated clotting time >300 s. Stented patients also received ticlopidine (250 mg·day⁻¹) or clopidgrel (75 mg·day⁻¹) for at least 1 month. Balloon angioplasty was performed according to standard clinical practice. After successful angioplasty, intracoronary β radiation was performed as previously described[11], and repeat angiography and intravascular ultrasound pullback were carried out. If the result was suboptimal (>30% diameter stenosis), or if the patient was assigned to provisional stenting, the stent was implanted with high-pressure post-dilatation and intravascular ultrasound guidance. Finally, repeat angiography and intravascular ultrasound were carried out. Intracoronary isosorbide dinitrates (200 µg) were administered immediately prior to each of the intravascular ultrasound pullbacks. At follow-up (6–8 months), further intravascular ultrasound analysis of the treated vessel was performed.

**Intravascular ultrasound image acquisition and quantitative analysis**

The coronary segment subject to three-dimensional reconstruction was examined with a mechanical intravascular ultrasound system (CVIS, Boston Scientific Corporation, Maple Grove, MN) with a sheath-based intravascular ultrasound catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of echocardiographic images (EchoScan, Tomtec, Munich, Germany). A description of this system has been reported in detail elsewhere[15–17]. In brief, the steering logic of the workstation considered the heart rate variability and only acquired images from cycles meeting a predetermined range and coinciding with the peak of the R wave.

A Microsoft Windows®-based contour detection program, developed at the Thoraxcenter, was used for
off-line volumetric quantification. Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen, media and stent boundaries. Volumetric data were calculated by the formula: 

\[ V = \sum_{i=1}^{n} A_i \cdot H, \]

where \( V \) = volume, \( A \) = area of EEM (external elastic membrane), lumen, stent or plaque in a given cross-sectional ultrasound image, \( H \) = thickness of the coronary artery slice, that was reported by this digitized cross-section, and \( n \) = the number of digitized cross-sectional images encompassing the volume to be measured. Checking and editing of the contours of the planar images were performed by two independent experienced analysts (K.K., M.C.). Intra-observer variability assessed by analysing intravascular ultrasound volumetric studies at least 3 months apart has been reported: 

\[-0.4 \pm 1.1\% \text{ in lumen volume, } -0.4 \pm 0.6\% \text{ in total vessel (EEM) volume and } -0.3 \pm 1.0\% \text{ in vessel wall (plaque+media) volumes using motorized ECG-gated pullback.}\]

The application of this system has been reported in clinical studies. The assessment of external elastic membrane in stented patients has been reported. When the radiation source train, balloon inflations and their relationship with anatomical landmarks. Typically, the aorto-ostial junction, stent and/or side-branches were used as landmarks. The anatomical landmark closest to either of the balloon markers was used as a reference point. During the subsequent intravascular ultrasound imaging, this reference point was recognized and used for selecting the area of interest: a 30-mm long segment irradiated by the radioactive or sham source train. At follow-up, correct matching of the region of interest was assured by both the use of the same intravascular ultrasound motorized pull-back system and comparison of the longitudinal view to that of post-procedure. In the radiation group, a 26-mm segment, which we considered as fully irradiated, was selected by excluding both 2-mm ends of the 30-mm segments between the two gold markers, because this radiation source has an acute dose fall-off starting at the last seeds. Similar analysis was performed in the control group. In stented vessels, a specific analysis only within the segment covered by the stent was also performed.

Total vessel (EEM), lumen and stent volumes were calculated from the contours of each cross-section by the software as stated above. In-vivo measurement of neointimal formation after stenting has been previously validated. The assessment of external elastic membrane in stented patients has been reported. When the EEM boundary was not visible in a single cross-sectional view, the computer interpolated it from the contours of the cross-sections immediately prior to and following. In addition, the use of three-dimensional reconstruction with multiple longitudinal views facilitated the visualization of vessel structures outside the stent. In all cases, the stented segment was covered by the radiation or dummy source. Since it is usually impossible to distinguish the intima and media by intravascular ultrasound, vessel wall volume (plaque plus media), tissue growth inside the stent, and vessel wall volume outside the stent were calculated as the representatives of tissue growth.

Vessel wall volume (plaque plus media): 

\[ \text{Total vessel (EEM) volume — Lumen volume} \]

Tissue Growth Inside Stent = 

\[ \text{Stent volume — Lumen volume within stent} \]

Vessel wall volume outside the stent = 

\[ \text{Total vessel volume of stent-covered segment — stent volume} \]

In order to assess the volumetric changes in the vessel structures after 6–8 months, the delta value for each measurement was calculated (delta (\( \Delta \)) = follow-up – post-procedure). To eliminate the influence of the vessel size and the length of the analysed segment, percent change (delta volume/post-procedure volume) was also calculated.

Remodelling of the vessel wall was considered when total vessel (EEM) volume increased or decreased, compared to post-procedure measurements by at least two standard deviations (\( \pm 1.2\% \)) of the intra-observer variability. By using this technique, the potential intrinsic error of the method may be avoided.

**Statistical analysis**

Quantitative data are presented as mean ± standard deviation. The comparisons between the volumetric data were performed using the two-tailed, paired or unpaired Student’s t-test. Categorical data were compared by means of Fisher’s exact test. A value of \( \text{P}<0.05 \) was considered statistically significant.

**Results**

Baseline clinical characteristics were similar between irradiated and control patients (Table 1). Lesion location was also similar between the irradiated and control groups (RCA 34% vs 39%, LAD 41% vs 39%, LCX 25% vs 22%, respectively).

**Clinical data**

No death and myocardial infarction was observed in the study populations. Restenosis (%diameter stenosis >50% by quantitative coronary angioplasty) was
**Table 1** Baseline patient characteristics. Values were not significant

<table>
<thead>
<tr>
<th></th>
<th>Radiation (n=40)</th>
<th>Control (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 10</td>
<td>58 ± 9</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>32 (80%)</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>History of MI</td>
<td>26 (65%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Diabetics</td>
<td>4 (10%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (35%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20 (50%)</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>26 (65%)</td>
<td>11 (61%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>17 (43%)</td>
<td>24 (44%)</td>
</tr>
<tr>
<td>Angina CCS III/VI</td>
<td>14 (70%)</td>
<td>14 (78%)</td>
</tr>
</tbody>
</table>

CAD=coronary artery disease; CCS=Canadian Cardiovascular Society angina class; MI=myocardial infarction.

observed in 6 out of 28 lesions (21%) in the irradiated balloon group and four out of 16 lesions (25%) in the irradiated stent group. Target lesion revascularization rates were 14% in the balloon group and 25% in the stent group. In the control group, two lesions (20%) in the balloon group and two lesions (25%) in the stent group presented restenosis. Target lesion revascularization rates in the control groups were 10% and 12.5%, respectively.

**Balloon vs stent within the irradiated segment**

There was no difference in baseline characteristics between balloon and stented patients. Volumetric data are demonstrated in Table 2. In the irradiated patients, EEM volume and vessel wall volume increased significantly by the paired t-test in both balloon and stented vessels during follow-up as shown in Fig. 1. The degree of EEM volume increase was similar between the balloon group and the stent group (+36.6 mm³ vs +42.3 mm³, P=ns). Accordingly, lumen volume remained unchanged in both groups (215·9 mm³ to 219·4 mm³ in the balloon group, 217·2 mm³ to 210·1 mm³, in the stent group, P=ns for both groups). Similar correlations of the % changes in lumen dimensions, tissue growth and vessel enlargement have been observed between balloon treated and stented vessels (Fig. 2).

**Irradiated vs control**

Percent changes in intravascular ultrasound parameters are presented in Fig. 3. In both balloon angioplasty and stenting vessels, positive remodelling (enlargement of the EEM volume) was observed more frequently in the irradiated group than in the control group (68% vs 30%; \( P=0.044 \)) in balloon treated vessels, 88% vs 25% (\( P=0.005 \)) in stented vessels. In the balloon treated segments, vessel enlargement fully compensated for the vessel wall volume increase so that the lumen even increased (+3.4%) in the irradiated vessels (Fig. 3). In the stented vessels of irradiated patients, vessel wall volume increased despite inhibition of tissue growth inside the stent (Fig. 3), owing to the total vessel volume increase. Thus lumen reductions were more pronounced in the control vessels than in the irradiated vessels after both balloon angioplasty and stenting (Fig. 3).

**Neointimal hyperplasia and vessel enlargement in stented vessels**

Percent reduction in lumen volume in segments not covered by the stent was similar to that in the irradiated segments covered by stent (-3.1% vs -7.8%, \( P=ns \)) as shown in Fig. 4. Total vessel (EEM) volume and vessel wall volume also increased similarly in both segments.

In the stent-covered segments, tissue growth inside the stent at follow-up was significantly smaller in the irradiated group than in the control group (8·0 ± 7·9 mm³ vs 26·8 ± 13·8 mm³, \( P=0·001 \), respectively), although the total amount of tissue growth was similar in both groups (Fig. 5). Different patterns of the tissue growth distribution was observed between irradiated and non-irradiated vessels. In the irradiated vessels, tissue growth mainly occurred outside the stent (25·1 out of 33·1 mm³), whereas most of the tissue increase in control vessels was represented by tissue growth inside the stent (26·8 out of 29·2 mm³) as demonstrated in Fig. 5.

**Discussion**

This 3-D volumetric intravascular ultrasound study demonstrates that catheter-based β-radiation induces...
vessel enlargement after both balloon angioplasty and stenting compared with controls. Positive remodelling was the main mechanism of preserving lumen volume after balloon angioplasty in the irradiated patients. In the stented vessels, neointimal formation was inhibited and the lumen preserved in the irradiated segments. However, vessel wall volume significantly increased outside the stent in the irradiated vessels.

It has been reported that vessel shrinkage is mainly responsible for restenosis after conventional balloon angioplasty\cite{26–29}. It has been shown that intracoronary radiation inhibited neointimal proliferation in most experimental models\cite{30–33}. In addition, experimental data have also suggested that radiation has an effect on vessel remodelling by modifying cell responses in the adventitia.\cite{11,12} In the irradiated group, 35 vessels (80%) had an increase in total vessel (EEM) volume. The thinning of the adventitial layer by radiation may be one of the explanations for this phenomenon, although it is still controversial\cite{33,34}.

In stented segments, the change in lumen volume was similar to that in non-stented segments in the irradiated vessels. Furthermore, the lumen was preserved regardless of the stent presence. These findings suggest that the coronary stent is not necessary for lumen maintenance in the setting of catheter-based radiation. Considering the fact that the combination of stent and radiation has been associated with late thrombosis\cite{34–36} and late stent malapposition\cite{37}, the implantation of coronary stents in the setting of intracoronary radiotherapy may be discouraged, unless it is a bail-out situation.

Judging from the results in the stented vessels, it seems that tissue grows only outwards after intracoronary irradiation and results in enlargement of the total vessel (Fig. 5). It has been suggested that intravascular radiation decreases myofibroblast differentiation in the adventitia and reduces cell proliferation without affecting apoptosis\cite{12}. Fareh has reported that β-radiation caused vascular smooth muscle cells to remain in the G0/G1 phase, and the growth arrest was maintained over 5 days. It has also been reported that the migratory function may be more radiosensitive than the proliferative response.\cite{38}. In our previous report, the average delivered dose at the adventitia was only 5Gy using the same system. Therefore, it is possible that while a considerable number of segments receive a lower dose than the effective dose for the inhibition of tissue growth, those doses are sufficient for the inhibition of migration in this study. The presence of stent metal stimulates the cellular response when the effect of radiation diminishes one week after the procedure\cite{11}. It has been shown that migration of smooth muscle cells into the intima did not contribute to lesion growth during the second week after injury\cite{39}. Thus, the second wave of cellular proliferation may not be inhibited by catheter-based radiation, and tissue proliferation may be more frequent on the outer layer of the media close to the adventitia rather than the intima in the irradiated vessels when migration of proliferative cells are inhibited. Further immuno-histochemical investigation is necessary to elucidate the mechanism of this finding.
Limitations

In human studies, it is almost impossible to distinguish the intima and media using intravascular ultrasound. The enlargement of the echogenic marker at the outer layer of media is assumed as positive remodelling. This study is not based on the actual dose calculated by the distance from the centre axis to the adventitia. Heterogenic distribution of the delivered dose, which is related to plaque growth, has been previously demonstrated in the setting of catheter-based radiation. Accurate dosimetry will provide important information to the mechanism of remodelling and the plaque increase process.

Studies using intravascular ultrasound are limited in cases where severe restenosis is present. However, only three patients were not included in this study for this reason. Vessels with multiple stents (n=10) were excluded from the analysis, since multiple stent deployment with overlapping or gaps between stents may be a confounding factor in the mechanistic interpretation of our results.

Conclusions

Intracoronary β-radiation induces vessel enlargement after balloon angioplasty and/or stenting, accommodating tissue growth. Additional stenting may not play an important role in the prevention of constrictive remodelling in the setting of catheter-based intracoronary radiotherapy.

The Wenckebach prize was awarded to P. W. Serruys by the Dutch Heart Foundation and is utilized for brachytherapy research in the catheterization laboratory. The authors appreciate the efforts of the catheterization laboratory staff, the radiation staff and the department of clinical epidemiology.

References

Figure 3  Percent volumetric changes in intravascular ultrasound parameters within fully irradiated segments. Comparison between irradiated (□ n=28) and control (■, n=10) vessels.

Figure 4  Percent volumetric changes in intravascular ultrasound parameters in stented vessels. Comparison between stent-covered (■) and uncovered (□) segments within fully irradiated segments.


