ORIGINAL ARTICLE

THE "EDGE EFFECT" AFTER IMPLANTATION OF β-EMITTING (^{55}CO) STENTS WITH HIGH INITIAL ACTIVITY

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Summary: The aim of this study was to evaluate the incidence and the cause of "edge restenosis" after implantation of high activity 41.1 μCi±1.2 μCi=1520 kBq±44 kBq, β-emitting (^{55}Co) stents. Proton bombarding in cyclotron has brought the radioactivity. Intravascular ultrasound (IVUS) investigation has been completed in 10 patients. The angiographies performed at 6 month revealed restenosis >50 % in 5 cases (50 %). The analysis of edges (5 mm distally and proximally to the last stent struts) showed no significant changes in TVV (187.3±62.60 mm^3 and 176.9±53.5 mm^3) but PMV increase significantly (i.e. neointimal proliferation) from 61.9±31.2 mm^3 to 82.2±43.4 mm^3 ($p<0.04$) and was the major contributor (from 66 %) to lumen volume loss (125.4±40.7 mm^3 and 94.7±22.2 mm^3, $p<0.02$). In conclusion, neither statistically significant positive nor negative remodelling at the "stent edges", were present. Statistically significant increase in plaque+media volume (i.e. neointimal hyperplasia) and reduction in lumen volume were found. The cause of "edge restenosis" was especially (from 66 %) due to increase in plaque+media volume (i.e. neointimal hyperplasia). Probably, main reason for "edge effect"/neointimal hyperplasia was in this trial sharp fall-off in radiation at the edges of the stents.

Key words: *Radioactive stents; Angioplasty; Remodelling; Intravascular ultrasound*

Implantation of conventional stents has reduced restenosis rates significantly, especially by minimizing of elastic recoil and preventing negative remodelling (3,12,14,18). However, massive neointimal proliferation and matrix synthesis as a response to the traumatizing intervention leads in in-stent restenosis in 25–50 % (3,12). Catheter-based intravascular brachytherapy, mainly from gamma and beta sources have been shown, in several experimental and clinical trials, to be a promising treatment in reducing restenosis rates, by inhibiting of smooth muscle cell proliferation and neointimal hyperplasia (21,19,22,8). The use of stents as bearer of radiation seems to be the simplest and the fastest way and several studies have demonstrated a dose-related reduction of in-stent restenosis, employing ^{32}P β-emitting radioactive stents with activity of 6–24 μCi=222–888 kBq (1,20). However, high rate of intralesion restenosis resulting in high target lesion revascularisation was seen in these trials, especially due to restenosis at the stent edges ("edge restenosis") (1,2). A fall-off in radiation is supposed to be a main possible mechanism in developing of this edge effect, probably combined with systemic balloon injury in the reference segment (especially using aggressive stent implantation strategy) and with so called "geographical miss".

The aim of this study was to evaluate the effect of high radioactive (mean 41.1 μCi±1.2 μCi=1520 kBq±44 kBq), β-emitting (^{55}Co) stents on neointimal tissue regrowth within stents and eventual plaque and vessel volume changes within the stent and in the adjacent artery segment, using serial IVUS analysis.

Methods

Patient selection

Based on research project, we started at our institution with implantation of radioactive (BX Velocity^{tm}), 18mm length stents, with high activity 41.1 μCi±1.2 μCi=1520 kBq±44 kBq brought by cyclotron. Patients with single, de-novo lesion, with length<15mm, without important side branch or angiographic presence of calcification at the spot of stenosis, and with objective evidence of ischemia were eligible. We analysed neointimal hyperplasia and vascular remodelling in 10 patients who had completed a 6-month angiographic follow-up with intravascular ultrasound study. The Medical Ethical Committee of the University Hospital Hradec Králové approved the study. All patients provided written informed consent before the procedure.

Implantation technique

The irradiated bare stent was mounted on balloon and then implanted with low pressure (8 atmospheres) without predilatation, thereafter, high pressure post dilatation has been performed with 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. One cardiologist has done all stent implantations.

Medication

The revascularisation has been performed on standard patient's medication with anteplatelet pre-treatment (ticlopidine) 3 days before procedure. Patients received 10 000 international units of heparin at the initiation of the procedure and activated clotting time was maintained at >300 seconds. All patients received aspirin 100 mg daily indefinitely and ticlopidine 500 mg daily for 6 months to avoid possible late occlusion.

Radioactive stents

The radioactivity has been brought by cyclotron at the Institute of nuclear physics of Czech academy of science in Řež. The main isotope of this radioactive stent is beta-emitter ^{55}Co with half-life time of 18 hours. Other radioisotops produced in the cyclotron except ^{55}Co were ^{56}Co, ^{57}Co, ^{52}Mn, ^{57}Ni and ^{96}Tc with half-lives between 18 hours (^{55}Co) and 270 days (^{57}Co). The activity of each radioisotops was 1.1 megabecquerel (MBq) for ^{55}Co, 0.01 MBq for ^{56}Co, 0.006 MBq for ^{57}Co, 0.11 MBq for ^{52}Mn, 0.32 MBq for ^{57}Ni and 0.01 MBq for ^{96}Tc. The dose, calculated for 0.1 mm depth of tissue, was 50–60 Gy and 75 % of this dose was delivered within first 72 hours. The initial activity of the stents was measured and when the activity had decreased to about 40 μCi=1,5 MBq, the stent had been implanted. The use of these radioactive was previously described only in animal study (4). The feasibility and safety of using ^{55}Co radioactive stents in human has been published recently (16).

Intravascular ultrasound image acquisition analysis

After the final balloon inflation and administration of intracoronary nitrates, IVUS has been performed with a mechanical IVUS system (Clear View, Cardio Vascular Imaging System, CVIS, Boston Scientific Corp, San Jose, CA) working with a sheath-based IVUS catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. The IVUS transducer was withdrawn through the stationer imaging sheath by automatic motorised pullback device at fixed speed 0.5mm/second to ensure a constant interval between slices allowing for accurate volumetric analysis. Ultrasound images were recorded on half-inch, high-resolution s-VHS videotape for off-line analysis. This was repeated at the 6-month follow-up.

Quantitative intravascular ultrasound analysis

The IVUS analysis was performed by one cardiologist with experience in IVUS analysis with intraindividual variability from last 100 consecutive IVUS analysis 1.3±2.7 % for LV, 1.9±3.1 % for total vessel volume TVV and 2.2±3.7 % for PMV. The investigated segment was not only stent, but also the adjacent coronary segment 5 mm distal and proximal to the stent. So, the length of analysed area was 28 mm. 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 plus 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). In our study the delineation of the total vessel volume boundary was possible in all IVUS analysed patients. All volumetric dates were calculated using the Simpson's formula: $V= \Sigma^{n}_{i=1} A_{i.} H$, where V=volume, A= area of external elastic membrane (EEM), lumen, stent or plaque in a given cross-sectional ultrasound image, H=thickness of the coronary artery slice, that was reported by this digitised cross-sectional IVUS image, and n=number of digitised cross sectional images encompassing the volume to be measured. Validity of this method has been proved previously (9).

The vessel remodelling was described as a change of total vessel volume (ΔTVV) during follow-up (TVV at 6 month follow-up minus TVV after procedure), similarly, ΔLV for lumen changes (LV at 6 months minus LV after procedure), ΔPMV for plaque and media volume (PMV at 6 months minus PMV after procedure), and ΔSV for eventual stent volume changes (late recoil) (SV at 6 months minus SV after procedure). NIHV is presented as a mean of neintimal hyperplasia volumes within the stents at 6-month follow-up.

Definition and segments of analysis

Stent edges were defined as those volumes axially 5 mm proximal and distal to the final stent strut, stent extremities as volumes axially 5 mm at the both edges of stents and stent body as 8 mm long middle part of stents. Restenosis was defined as an agiographic restenosis >50 % at 6-month follow-up located either at stent edge or stent itself.

Statistical analysis

Quantitative data are presented as a mean ± standard deviation. Volumetric date derived from the IVUS investigations were compared immediately after treatment and at follow-up using the two-tailed paired Student's t-test. A value of $p<0.05$ was considered statistically significant.

Results

Baseline clinical and procedural characteristics are described in Table 1. Table 2 describes quantitative coronary angiography data pre- and post-intervention and at 6-month follow-up. At 6-month follow-up, no myocardial infarctions,

Tab. 1: Clinical and Procedural Characteristic.

N	10
Age (mean)	55 (50–71)
Male (%)	70
Prior MI (%)	50
Unstable angina (%)	30
Smoking (%)	50
Hypercholesterolemia (%)	70
Family history (%)	20
Hypertension (%)	60
Diabetes (%)	50
Vessel LAD	6
LCx	1
RCA	3
Lesion length (mm)	8.2±2.5
Balloon length-post (mm)	14.4±1.9
Final balloon size (mm)	3.9±0.5
Max inflation pressure[1] (atms)	8.0±0
Max inflation pressure[2] (atms)	15.1±2.8
Balloon-to-artery ratio	1.14

LAD=left anterior descending coronary artery, LCx=left circumflex artery, RCA=right coronary artery.
Max inflation pressure[1]=balloon at time of stent implantation
Max inflation pressure[2]=balloon inflation within stent

Tab. 2: Angiographic data.

	Pre	Post	FU
MLD	0.96±0.37	2.98±0.44	2.21±0,47
DS	70±12	19±6	53±21
RD	3.25±0.38	3.29±0.46	3.17±0.41
Acute gain		2.02±0.52	
Late loss			1.55±0.44
Type of restenosis, n (%)			
Intrastent-focal	1 (10)		
Total occlusion	0 (0)		
At the edge	5 (50)		

FU=6 month follow-up.
MLD=minimum lumen diameter, DS=diameter stenosis, RD=reference diameter

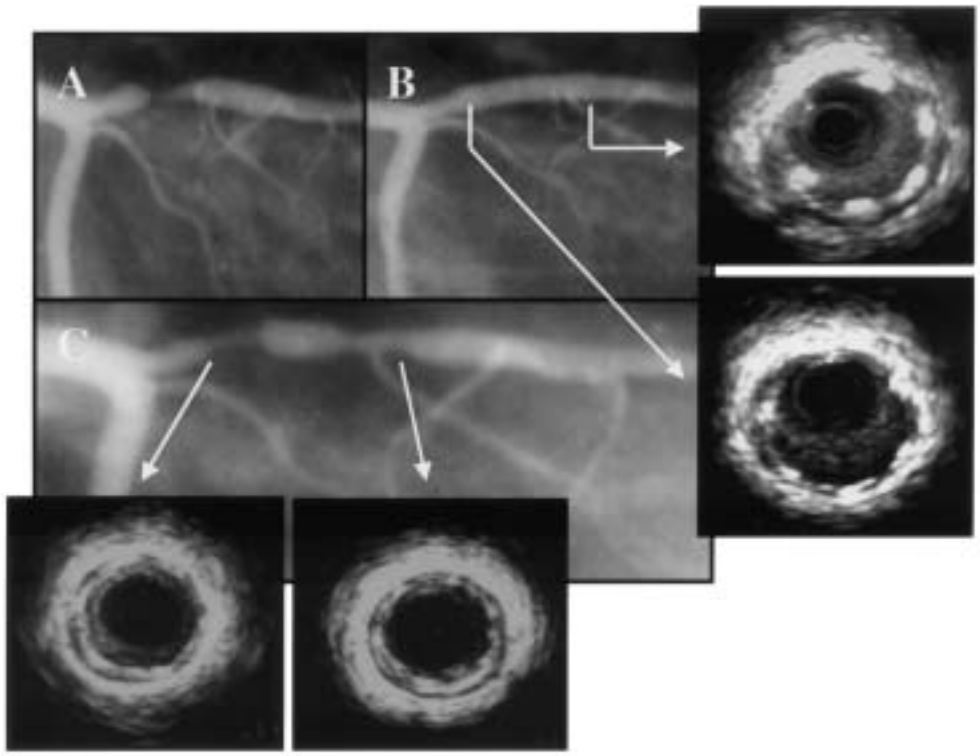

Fig. 1: Pattern of "a candy wrapper" stenosis at 6-month follow-up. Initial stent activity was 37.05 μCi.
Initial angiography (A) showing a severe proximal LAD stenosis. An optimal angiographic result after implantation of radioactive stent is presented (B). IVUS images demonstrating good stent apposition to the vessel wall at both, distal and proximal stent extremities. (C) A 6-month angiography revealed restenosis at the both edges. IVUS showing as well as huge amount of NIH at the both stent extremities.

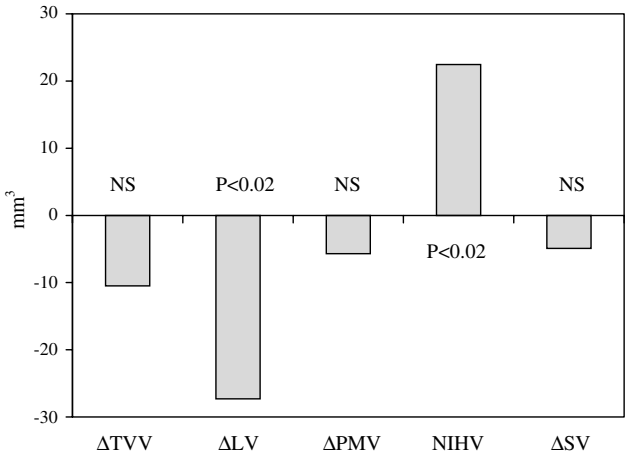

Fig. 2: Remodelling within the margins of the stent at 6-month.
Significant decrease in lumen volume and increase in NIH (both edges together) was found at 6-month follow-up. ΔTVV=changes in total vessel volume, ΔLV=changes in lumen volume, ΔPMV=changes in plaque and media volume, NIHV=neointimal hyperplasia volume, ΔSV=changes in stent volume.
NS=not significant

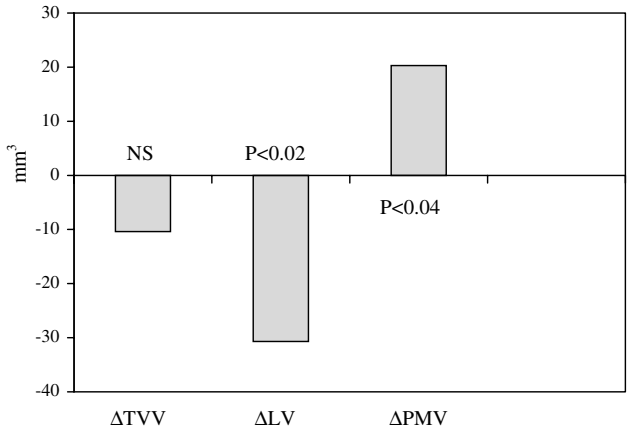

Fig. 3: Remodelling at the edges at 6-month.
Significant decrease in lumen volume (ΔLV) was mainly due to plaque accommodation (neointimal proliferation) (ΔPMV). No-significant changes in total vessel volume (ΔTVV) were found.

Tab. 3: Mean (SD) volumes within the stents and at the edges (n=10) (mm^3).

	TVV b	TVV a	LV b	LV a	PMV b	PMV a	NIH
Stent	353.6 (126.3)	343.1 (90.6)	181.9 (80.2)	154.6 (45.2)*	171.7 (57.4)	166.0 (42.6)	22,45 (21,9)*
Edges	187.3 (62.6)	176.9 (53.5)	125.4 (46.7)	94.7 (22.0)*	61.93 (45.2)	82.3 (43.4)*	

TVV=total vessel volume, LV=lumen volume, PMV=plaque+media volume, NIH=neointimal hyperplasia.
b=after stent implantation
a=at 6-month
*=statistically significant (p<0.05)

deaths, or stent thrombosis was seen. The angiography revealed restenosis >50 % in 5 cases (50 %). Distal edge restenosis developed in two cases, proximal edge restenosis also in two cases and in one case a "candy wrapper" restenosis was present (Fig. 1). Target lesion revascularisation was performed in three patients (30 %) with objective evidence of ischemia: Two patients with angiographically significant stenosis (>50 %) were not revascularized. One patient refused repeat procedure and second had no evidence of ischemia in spite of angiographic restenosis >50 %. One patient was revascularized due to progression of coronary artery disease with stenosis >50 % at the non-treated segment at 6-month of follow-up. So, the target vessel revascularisation was done in four patients (40 %). IVUS analysis (Fig. 2 and Tab. 3) demonstrated an absence of remodelling behind the stent, with no significant changes in TVV (353.6±126.3 mm^3 and 343.9±90.6 mm^3) or plaque volumes (171.7±57.4 mm^3 and 166.8±42.6 mm^3). On the contrary, the LV within the stent decreased significantly from 181.9±80.2 mm^3 to 154.6±45.2 mm^3 (p<0.02). It means reduction of stent lumen volume by 15 % at 6-month. This was due to presence of NIH at both extremities (more but no statistically significant at distal part) of implanted stents. The ingrowth of NIH was inhibited at the body (8 mm long segment in the middle part of the stent) of stents compared to extremities (5mm long segment at each end) of the stents (7.3±5.9 mm^3 versus 28.4±26.2 mm^3, p<0.05). Also, no chronic recoil of the implanted stents was seen in this group (181.9±80.2 and 177.0±56.2 mm^3). The analysis of edges (5mm distally and proximally to the last stent struts) showed no changes in TVV (187.3±62.6 mm^3 and 169.9±53.5 mm^3) but PMV increase significantly from 61.9±31.2 mm^3 to 82.2±43.4 mm^3 (p<0.04) and LV decreased from 125.4±40.7 mm^3 to 94.7±22.0 mm^3 (p<0.02) (Fig. 3). This late lumen volume loss was mainly (from 66 %) due to increase in PMV.

Discussion

The results of this study indicate that using single, 18 mm-long, ^{55}Co radioactive ß-emitting BX Velocity^{tm} stents with high initial activity 41.1 μCi±1,2 μCi=1520 kBq±44 kBq has no beneficial effect in prevention of restenosis in spite of meticulous alertness not to injured the vessel segment proximal and distal to the stent. This no beneficial effect was mainly due to edge restenosis, which was found in five out of ten patients (50%) and due to exuberating NIH at both stent extremities, predominantly localised at the distal edges.

Edge restenosis was mainly due to plaque accommodation. In these high radioactive stents, the neointimal formation was inhibited only in the body of the stents.

Mechanism of edge restenosis

In our study, the edge restenosis with significant late lumen loss was mainly due to an increase in plaque and less due to vessel remodelling. This is with agreement of results published by Kay et al. (6), describing that for stents with activity 6–12 μCi=222–444 kBq is plaque accommodation (neointimal proliferation) the major contributor to lumen loss. On the opposite, Albiero et al. (2) concluded in their study that edge restenosis was mainly due to shrinkage of the vessel for stent with initial activity 12–21 μCi=444–777 kBq.

Since all stents in our study were implanted employing a "nonaggressive strategy" (low pressure without predilatation and high pressure postdilatation has been done with a shorter balloon) we supposed that "geographical miss" was minimize (but "some" balloon injury at the stent ends is always) and so we strongly believe that the edge effect in this trial was mainly due to fall-off in radiation at the edges of the stents.

In agreement with other studies (6), no statistically significant chronic recoil of the stent was found.

Future directions

Two different modalities have been proposed to solve the problem of edge restenosis: the hot-ends or the cold-ends stents. The hot-ends stents involve literally concentrating the greatest activity at the stent edges. The background for this approach was to extend the area of irradiation beyond the balloon-injured area outside the stent, thereby decreasing the chance of geographical miss (13). However, it has been proved, that subtherapeutic levels of radiation can stimulate proliferation or remodelling in uninjured vessel segments in animal model (10) and so, it might be that increasing the activity at the stent ends will only postpone the restenosis further from the stent. The cold ends stent is another modality. If the edge restenosis is result of negative remodelling (induced by low-dose radiation in an injured area), then the lengthening of the stent could be solution to prevent this negative remodelling. But, this concept was denied by Rotterdam group by publishing their results concerning use of cold-end radioactive stents (7). They found increased neointimal hyperplasia in in-stent non-radioactive segments ($p<0.017$).

According to our study or other latest data and with agreement of others (20,11) we can postulate that use of radioactive stents is safe and feasible but, at present, the problem of edge restenosis remains unsolved and so, these stents should not be clinically used.

However, further therapeutic options are coming on the horizon with promising preliminary data such as drug-eluting stents with rapamycin or paclitaxel (15,5) or biodegradable stents (17).

Conclusion

Single ^{55}Co radioactive β-emitting stents with high initial activity 41.1 μCi±1,2 μCi=1520 kBq±44 kBq are effective in reducing of neointimal hyperplasia only within the stent body, as measured by IVUS, and they do not solve the problem of restenosis at the stent extremities as well as at the stent edges. Edge restenosis in this high radioactive stents was mainly (from 66%) due to neointimal proliferation.

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