

## Cutting Balloon Angioplasty versus Conventional Balloon Angioplasty for In-Stent Restenosis Treated by Intracoronary Radiation Therapy

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### ABSTRACT

**Background:** Cutting Balloon angioplasty (CBA) may be a useful treatment modality for in-stent restenosis (ISR) as it maintains a stable position during dilatation and results in potentially less injury than plain old balloon angioplasty (POBA). The purpose of this study was to compare CBA and POBA with intracoronary radiation therapy (IRT) for in-stent restenosis (ISR). **Methods:** We selected 157 consecutive patients from the WRIST (Washington Radiation for In-stent restenosis Trial) series of gamma radiation trials using both gamma and beta emitters for ISR of native coronaries or saphenous vein grafts, who were treated with CBA or POBA as the only treatment strategy before intracoronary radiation therapy. Patients in the CBA (N=64) and POBA (N=93) groups were matched for baseline demographic and procedural characteristics. Radiation was delivered successfully in all cases. **Results:** At angiographic follow up, acute gain was higher in the CBA group than the POBA group ( $1.7 \pm 0.7$  mm vs.  $1.4 \pm 0.9$  mm,  $p=0.03$ ). The angiographic restenosis rate (17.1% vs. 23.5%,  $p=NS$ ) and edge restenosis rate (6.3% vs. 12.2%,  $p=NS$ ) were not significantly lower in the cutting balloon cohort. At a 6 month clinical follow up, the CBA group showed a statistically decreased rate of clinically driven target vessel revascularization compared to the POBA group (5.7% vs. 18.3%,  $p=0.038$ ). **Conclusions:** Cutting balloon angioplasty is a reasonable treatment strategy for in-stent restenosis prior to intracoronary radiation therapy. (Korean Circulation J 2004;34(1):28-34)

**KEY WORDS:** Cutting balloon; Brachytherapy; Coronary restenosis; Stents.

### Introduction

With over 800,000 stents a year in the U.S. only, in-stent restenosis (ISR) has become a significant iatrogenic problem. In-stent restenosis results primarily from neointimal tissue hyperplasia distributed either focally or diffusely over the entire length of the stent.<sup>1)</sup> Neointimal tissue must be mechanically removed or displaced before

radiation therapy can be delivered.<sup>2,3)</sup> However, many studies of in-stent restenosis have shown that no treatment modality was found to be superior and that all treatments lead to approximately the same re-restenosis rate.<sup>4-7)</sup> The device selection did not influence late clinical outcomes in in-stent restenosis treated by intracoronary gamma radiation therapy. Recent studies suggested that the cutting balloon angioplasty may be superior to conventional balloon angioplasty for the treatment of in-stent restenosis.<sup>8,9)</sup> The cutting balloon provides a stable position during balloon inflation and results in potentially less injury with the avoidance of the watermelon seeding effect compared to the conventional balloon. The purpose of this study was to assess the efficacy of cutting balloon

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angioplasty for patients with in-stent restenosis compared to conventional balloon angioplasty when both are treated with intracoronary radiation therapy.

## Methods

### Study population

We analyzed 157 patients who were enrolled in the WRIST (Washington Radiation for In-Stent restenosis Trial) series of radiation trials for ISR using gamma and beta emitters at the Washington Hospital Center between January 2000 and April 2001. These trials were designed to test the effectiveness of IRT as adjunctive treatment to the conventional intervention of ISR (Table 1). The subjects included 157 patients treated with IRT where each had received a completed 6-months clinical follow-up. All studies involved an Investigational Device Exemption granted by the Food and Drug Administration

and were approved by the Institutional Review Board and the Radiation Safety Committee at the Washington Hospital Center. Informed consents were obtained for all patients.

All clinical events were independently adjudicated by an external committee. The inclusion criteria for the initial IRT index procedure included ISR, lesion diameter stenosis >50% in the presence of angina or inducible ischemia on functional testing, reference vessel diameter of 2.5–5.0 mm, lesion length <80 mm, and a successful primary coronary intervention. Exclusion criteria included acute myocardial infarction within 72 hours of the index procedure, left ventricular ejection fraction <20%, angiographic visible thrombus, multiple coronary lesions, and prior coronary or chest radiation therapy.

### Interventional procedures

All patients were pretreated with 325 mg of aspirin and antiplatelet therapy with either 250 mg of ticlopidine taken orally two times per day or 75 mg of clopidogrel daily for 1 to 6 months depending on the study protocol. Preceding the percutaneous coronary artery or saphenous vein graft intervention, an angiogram and an intravascular ultrasound study were performed to determine the lesion length and vessel size. Device selection was based on lesion morphology and was at the discretion of the operator in an attempt to optimize the final angiographic or intravascular ultrasound result. We analyzed patients who were treated with cutting balloon and conventional balloon and excluded those patients treated with excimer laser, rotational atherectomy, and re-stenting.

### Cutting balloon angioplasty

The cutting balloon, developed by Barath<sup>10)</sup> and manufactured by IVT (Interventional Technologies, San Diego, California) is a system that combines the features of conventional balloon angioplasty with advanced microsurgical capabilities. The system consists of a compliant balloon 10 or 15 mm in length with 3 or 4 microtome-sharp atherotomes (microsurgical blades), depending on balloon size, are bonded longitudinally to the balloon

**Table 1.** Study population with emitters and doses

Radiation study	Emitter	Dose (Gy)	CBA (n=64)	POBA (n=93)
ARTISTIC	Ir-192	18 at 2 mm	8	2
SVG-WRIST	Ir-192	15 at 2 mm	0	6
Long WRIST high dose	Ir-192	18 at 2 mm	1	9
WRIST PLUS	Ir-192	15 at 2 mm	0	5
WRIST 12	Ir-192	15 at 2 mm	1	16
GAMMA-5	Ir-192	14 at 2 mm	5	2
Integrilin WRIST	Ir-192	15 at 2 mm	15	8
BRITE I, II	32-P	20 at 1mm	15	8
Compassionate WRIST	Ir-192	15 at 2mm	12	31
START & START 40/20	90-Sr	12 at 2mm	0	1
Galileo INHIBIT	32-P	20.6 at 1mm	16	3

ARTISTIC: angiorad radiation technology for in-stent restenosis trial in native coronaries, WRIST: Washington radiation for in-stent restenosis trial, SVG-WRIST: Washington radiation for in-stent restenosis trial for saphenous vein grafts, WRIST 12: Washington radiation for in-stent restenosis trial with 12 months of clopidogrel, BRITE: beta radiation to prevent in-stent restenosis, START: stents and radiation therapy, INHIBIT: intimal hyperplasia inhibition with beta in-stent trial, CBA: cutting balloon angioplasty, POBA: plain old balloon angioplasty

surface. The atherotomes, ~ 0.25 mm in height, are 3–5 times sharper than conventional surgical blades. As the cutting balloon is inflated, the atherotomes expand radially and incise the plaque, relieving its hoop pressure. This creates a fault line for dilatation to occur, which ensures that crack propagation proceeds in a more controlled fashion.

#### Clinical follow-up

Data was prospectively recorded and forwarded to the data-coordinating center (Cardiology Research Institute Data Analysis Center at the Washington Hospital Center, Washington, DC). Baseline clinical, procedural, in-hospital, and 6 month follow-up details were recorded. The 6-month follow-up period was taken as within 220 days of the index procedure to ensure that all patients were included in the analysis. The baseline clinical demographics and the in-hospital course were collaborated by an independent hospital chart review, performed by the data-coordinating center. Medical records with procedural and management details during subsequent admissions including repeat coronary interventions were obtained from the relevant hospitals. An adjudication committee independently reviewed the clinical events in all patients.

#### Radiation protocol

Patients were included from the WRIST (Washington Radiation for In-Stent restenosis Trial) series of radiation trials which had a similar design to the original WRIST protocol and commercial studies (Table 1). In preparation for the IRT treatment, each patient was further sedated, with the activated clotting time maintained at >300 seconds with intravenous heparin. The gamma (192-Iridium) and beta (90-Yttrium) IRT treatments in the WRIST studies have been previously described.<sup>11)12)</sup> A radiation oncologist was responsible for handling the radiation source, a radiation physicist was integral in dose calculation, and a radiation safety officer ensured adequate safety precautions were taken during the radiation dwelling period. A final angiogram was performed, and if required, further intervention was undertaken to

optimize the final results. Routine post care included cessation of heparin, early sheath removal, and in addition to aspirin, antiplatelet therapy.

#### Definitions

Procedural success was defined as <50% stenosis without major in-hospital complications (death, myocardial infarction, or coronary artery bypass surgery). Lesions were classified according to the modified ACC/AHA lesion classification score.<sup>13)</sup> Death was defined as all-cause mortality. Q-wave and non-Q-wave myocardial infarctions (MI) were defined as a total creatinine kinase elevation  $\geq 2 \times$  normal value and/or elevated creatinine kinase MB fraction  $\geq 20$  ng/mL with or without new pathological Q waves (>0.4 msec) in two or more contiguous leads. Target lesion revascularization (TLR) and target vessel revascularization (TVR) were characterized by repeat percutaneous coronary intervention (PCI) or Coronary Artery Bypass Grafting (CABG) involving the treated vessel, which is driven by clinical signs of ischemia in the presence of angiographic restenosis. Major adverse cardiac events (MACE) were defined as death, Q-wave MI, or TVR. Late total occlusion (LTO) was defined as an angiographically documented total occlusion at the lesion site >30 days of the index procedure.

#### Angiographic analysis

The Washington Hospital Center angiographic core laboratory performed a quantitative angiography using the CMS-GFT system (Medis, Netherlands). Angiographic analysis was performed on patients requiring percutaneous re-intervention of the target lesion, and a comparison was made to the angiogram of the index procedure. The minimal luminal diameter was determined for the total analyzed segment (5 mm proximal and distal to the irradiated segment). The reference vessel diameter, pre-procedural diameter, and post-procedural diameter stenoses after the intervention were calculated. Edge restenosis was defined as a follow-up diameter stenosis  $\geq 50\%$  occurring  $\leq 5$  mm proximal or distal

**Table 2.** Baseline demographics characteristics

	CBA (n=64)	POBA (n=93)	p
Age (years)	54±23	52±25	NS
Males (%)	71.9	68.8	NS
Smoking (%)	53.1	52.7	NS
Hypertension (%)	67.7	78.5	NS
Diabetes (%)	35.9	50.5	NS
Hypercholesterolaemia (%)	89.1	87.1	NS
Unstable angina (%)	94.6	96.1	NS
Previous MI (%)	45.3	40.9	NS
Previous CABG (%)	31.4	50.6	NS
Multivessel disease (%)	26.7	39.7	NS
LV ejection fraction (%)	51±11	50±14	NS

CBA: cutting balloon angioplasty, POBA: plain old balloon angioplasty, MI: myocardial infarction, CABG: coronary artery bypass graft, LV: left ventricle

**Table 3.** Lesion characteristics

	CBA (n=64)	POBA (n=93)	p
Vessel treated (%)			
Left main	3.2	5.5	NS
LAD	42.9	33.0	NS
LCX	20.6	20.9	NS
RCA	25.4	24.2	NS
Saphenous vein graft	7.9	16.5	NS
ISR type (%)			
Diffuse	67.9	71.8	NS
Focal	32.1	28.2	NS
Total occluded	2.5	5.1	NS

LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, ISR: in-stent restenosis

to the last seed of the radiation source.<sup>14)</sup>

### Statistical analysis

Statistical analysis was performed using the StatView statistical package (StatView 5, SAS Institute, Cary, North Carolina). Continuous variables were expressed as means±SD, categorical data as percentages. To analyze the efficacy of cutting balloon angioplasty, the Student's t-test was used to compare continuous variables,

and  $\chi^2$  test or Fisher's exact test were used to assess discrete variables. A value of  $p<0.05$  was considered significant.

## Results

### Baseline clinical characteristics and procedural details

The study population included a total of 157 patients with 111 patients (70.7%) being treated with gamma radiation and 46 patients (29.3%) being treated with beta radiation. Of all the patients, 64 patients were treated with cutting balloon angioplasty, and 93 patients were treated with conventional balloon angioplasty. Baseline clinical characteristics between the 2 groups were similar (Table 2). In the cutting balloon angioplasty group, the total radiation dose was  $14.7\pm0.5$  Gy. Procedural success was achieved in all patients. The difference in the incidence of in-hospital MACE between the 2 groups did not reach statistical significance (0% vs. 2.8%,  $p=0.22$ ). There were no statistically significant differences in lesion characteristics between the 2 groups (Table 3). In the conventional balloon cohort, the diffuse type of ISR was 67.9%, focal type ISR was 32.1%, and total occluded was 2.5%, whereas in the conventional balloon group, the diffuse type of ISR was 71.8%, focal type ISR was 28.2%, and total occluded was 5.1%.

### Angiographic characteristics

The angiographic follow up rate was 51.6% in the cutting balloon angioplasty group and 45.1% in the conventional balloon angioplasty group. There were no statistically significant differences in baseline angiographic measurements between the 2 groups (Table 4). After the intervention, the acute gain was greater in the cutting balloon angioplasty group than the conventional balloon angioplasty group ( $2.0\pm0.7$  vs.  $1.5\pm0.7$  mm,  $p<0.05$ ). The late loss showed no significant difference between the 2 groups ( $0.6\pm0.9$  vs.  $0.5\pm0.8$  mm,  $p=NS$ ), which showed wide variation of the data. The angiographic restenosis rate (17.1% vs. 23.5%,  $p=NS$ ) and edge restenosis rate (6.3% vs. 12.2%,  $p=NS$ ) were insignifi-

**Table 4.** Angiographic characteristics

	CBA (n=64)	POBA (n=93)	p
Reference vessel diameter (mm)	2.8± 0.6	2.9± 0.6	NS
Lesion length (mm)	19.7± 10.2	21.5± 13.4	NS
Pre diameter stenosis (%)	80.7± 14.2	76.7± 14.3	NS
MLD (mm)			
Pre	0.6± 0.5	0.8± 0.5	NS
Post	2.3± 0.7	2.2± 0.5	NS
Follow up	2.1± 0.9	1.9± 0.8	NS
Acute gain (mm)	1.7± 0.7	1.4± 0.9	<0.05
Late loss (mm)	0.6± 0.9	0.5± 0.8	NS
Angiographic restenosis (%)	17.1	23.5	NS
Edge restenosis (%)	6.3	12.2	NS
Total radiation dose (Gy)	14.7± 0.5	14.3± 0.5	NS

MLD: minimal luminal diameter, CBA: cutting balloon angioplasty, POBA: plain old balloon angioplasty

**Table 5.** 6-Month clinical outcomes

Outcomes (%)	CBA (n=64)	POBA (n=93)	p
Death	0	1.4	0.80
QMI	0	0	—
NQMI	1.9	4.2	0.47
TLR	5.7	14.1	0.13
TVR	5.7	18.3	0.038
LTO	1.9	4.2	0.47
MACE (TVR)	5.7	18.3	0.038

QMI: Q-wave myocardial infarction, NQMI: non-Q-wave myocardial infarction, TLR: target lesion revascularization, TVR: target vessel revascularization, LTO: late total occlusion, MACE: major adverse cardiac events

cantly lower in the cutting balloon cohort.

### 6-Month clinical outcomes

The numbers and frequencies of clinical events at 6 months among the entire cohort is outlined in Table 5. Deaths were not different between the 2 groups. Myocardial infarction rates were 0% in both groups. Non Q wave MI was 1.9% in the cutting balloon angioplasty group and 4.2% in the conventional balloon angioplasty group. The TLR was 5.7% in the cutting balloon angio-

plasty group and 14.1% in the conventional balloon angioplasty group. TVR and MACE TVR were 5.7% in the cutting balloon angioplasty group and 18.3% in the conventional balloon angioplasty group (p=0.038).

## Discussion

This study demonstrated an angiographically more acute gain and a reduction in clinically driven target vessel revascularization with cutting balloon angioplasty compared to conventional angioplasty for in-stent restenosis (ISR) that was treated with intracoronary radiation therapy.

Intracoronary radiation therapy is now an approved treatment for ISR. There are three treatment strategies for ISR before intracoronary radiation therapy, such as conventional balloon angioplasty, mechanical debulking (rotational atherectomy, eximer laser coronary angioplasty, directional coronary atherectomy), and additional stent implantation. However, the device selection did not influence late clinical outcomes in patients receiving adjunctive intracoronary radiation therapy for ISR.<sup>15)</sup>

Recently, cutting balloon angioplasty has been successfully utilized for the treatment of ISR.<sup>16)</sup> The cutting balloon achieves an efficient lumen gain by creating a controlled dissection within the vessel wall. The combination of incision and dilation of the plaque during cutting balloon inflation supposedly favors a more controlled rupture of the plaque, minimizes the vascular trauma, and decreases the subsequent intimal hyperplasia and restenosis.<sup>17)</sup> Cutting balloon angioplasty offers a novel and simple strategy for coronary lesions, resistant to conventional balloon angioplasty, by the controlled dissection of microsurgical blades which first score the resistant plaque. IVUS demonstrates specific lesion characteristics including fibrosis and calcification, which are two factors that favor the use of the cutting balloon than the conventional balloon.<sup>18)19)</sup>

The proposed mechanism of action of cutting balloon angioplasty in ISR is, first, cutting or scoring the neointimal, which lessens the elastic and fibrotic continuity of

the internal fibrous layer and then making the tissue more amenable to being pushed outward through the stent struts, given the fact that the presence of a large number of smooth muscle cells is likely to offer greater resistance to dilation and greater recoil. The mechanisms for lumen enlargement with the cutting balloon angioplasty are plaque extrusion through the stent struts and plaque disruption produced by the alignment of the blades. Suzuki et al. showed that the 63% of lumen enlargement was due to plaque compression and 37% was due to vessel expansion, whereas in the conventional angioplasty group, 27% was due to plaque compression and 73% was due to vessel expansion.<sup>20)</sup> IVUS assessment of the mechanism for lumen enlargement by cutting balloon angioplasty explained that the neointimal hyperplasia extruding out of the stent through the stent struts and also explained the longitudinal redistribution of the neointimal hyperplasia into the contiguous reference segments. However, IVUS could not determine whether this axial redistribution of in-stent neointima was neointimal tissue or persistent plaque.<sup>21)</sup>

Some studies have shown that cutting balloon angioplasty demonstrated better acute and follow-up angiographic results for in-stent restenosis compared to conventional balloon angioplasty.<sup>22)</sup> Cutting balloon angioplasty may be effectively utilized as adjunctive treatment strategies for in-stent restenosis before radiation therapy. The potential advantages of using the cutting balloon over conventional balloon angioplasty as the main interventional modality for in-stent restenosis before radiation therapy include the stable balloon position with no slippage during inflation and associated with this, a shorter length of injury from the so called “watermelon seeding effect” that is common after conventional balloon angioplasty.

Clinical studies have shown that adhesion molecules, Mac-1 (CD11b/CD18) and CD11b, which is upregulated on the surface of neutrophils after angioplasty, were significantly smaller in the cutting balloon compared to conventional balloon indicating that cutting balloon angioplasty injures the vessel wall less than conventional

balloons angioplasty.<sup>23)</sup> This theoretical advantage could avoid injury to the proximal and distal edge of the stent which is an important component of edge effect that is relevant complication of intracoronary radiation therapy. In our study, edge restenosis was presented to be 6.3% in the cutting balloon angioplasty and 12.2% in the conventional balloon angioplasty cohort, where no statistically significant difference was shown between the 2 groups.

Our study demonstrated a reduction in the clinically driven target vessel revascularization with cutting balloon angioplasty compared to conventional angioplasty for ISR that was treated with intracoronary radiation therapy.

#### Limitations of the study

This was a retrospective study and, therefore, contains all the disadvantages of such a comparative analysis. Operator’s bias clearly occurred in the selection of devices. In the cutting balloon angioplasty group, all of the patients were treated with cutting balloon and subsequently with conventional balloon. There were not design to test any efficacy of different devices during PCI.

#### Conclusions

Cutting balloon angioplasty, compared to conventional angioplasty, can help avoid balloon slippage during inflation and provide less injury, and thus, it is a reasonable treatment strategy for in-stent restenosis before intracoronary radiation therapy. This study demonstrated a reduction in the clinically driven target vessel revascularization with cutting balloon angioplasty compared to conventional angioplasty for ISR that was treated with intracoronary radiation therapy.

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