Randomized trial of conventional balloon angioplasty versus cutting balloon for in-stent restenosis. Acute and 24-hour angiographic and intravascular ultrasound changes and long-term follow-up

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Key words:
Coronary angioplasty; Coronary stent; Intravascular ultrasound; Restenosis.

Background. **The aim of this study was to investigate the angiographic and intravascular ultrasound (IVUS) changes following cutting balloon (CB) and percutaneous transluminal coronary angioplasty (PTCA) treatment in in-stent restenosis.**

Methods. **Fifty consecutive patients with in-stent restenosis were randomized to treatment with CB (n = 25) or PTCA (n = 25). The size of the device was selected using IVUS according to a 1:1 device-to-stent ratio and balloons were inflated to a maximal pressure of 8 atm. Quantitative coronary angiography (QCA) and IVUS (both planar and volumetric) evaluations were carried out before and after treatment and 24 hours later. In case of suboptimal results at 24 hours (≥ 50% diameter stenosis at QCA and/or ≤ 4.7 mm^2 minimal lumen area [MLA] at IVUS), the patients were re-randomized to receive additional treatment (CB for PTCA and vice versa) or to follow-up. Measurements included the minimal lumen diameter and diameter stenosis for QCA and the external elastic membrane area (EEMA), stent area (SA), MLA, restenosis area (RA = SA - MLA) and plaque + media area (PMA = EEMA - SA) for IVUS.**

Results. **A similar minimal lumen diameter increase (1.19 ± 0.44 vs 1.37 ± 0.55 mm) and diameter stenosis decrease (-37 ± 14 vs -45 ± 13%) was found after PTCA and CB. No significant difference was found in MLA increase (4.81 ± 1.9 vs 5.45 ± 2.0 mm^2) and RA decrease (-3.8 ± 1.3 vs -4.2 ± 1.7 mm^2) in PTCA and CB. SA, EEMA and PMA did not significantly change after treatment in either group. Of the total mean lumen enlargement after PTCA and CB, 20% was due to additional stent expansion and 80% was due to RA decrease. At 24 hours, a greater minimal lumen diameter increase (-0.23 ± 0.34 vs -0.06 ± 0.23 mm, p = 0.03) and MLA loss (-1.9 ± 1.4 vs 0.37 ± 0.8 mm^2, p = 0.000) and RA increase (1.74 ± 1.3 vs 0.37 ± 0.52 mm^2, p = 0.000) were detected in PTCA vs CB. Volumetric changes paralleled planar IVUS variations. A suboptimal result was more frequently found in PTCA as compared to CB (36 vs 4%, p < 0.01). At follow-up, PTCA had a higher target lesion revascularization as compared to CB (40 vs 12.5%, p < 0.05).**

Conclusions. **In in-stent restenosis, PTCA and CB share similar effects and mechanisms of lumen enlargement. In-stent tissue is mainly redistributed along a larger stent rather than being extruded out of the stent struts. At 24 hours, a significant lumen loss (instant restenosis) occurred more frequently in PTCA as compared to CB and may account for a higher target lesion revascularization in this group.**

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Introduction

Repeat percutaneous transluminal coronary angioplasty (PTCA) is the most common treatment employed for in-stent restenosis[1-3]. However, a recurrence rate > 50% has been reported especially in patients with angiographically diffuse or occlusive in-stent restenosis[1-3]. Debulking techniques such as laser angioplasty and directional or rotational atherectomy did not demonstrate any significant advantage over conventional PTCA[1,4-6]. The cutting balloon (CB) (Boston Scientific, Natick, MA, USA) has been recently proposed as an alternative device for in-stent restenosis. The unique feature of this device is the presence of 0.25-mm microblades (3 to 4 depending on the balloon size) bonded longitudinally on the balloon surface. These microatherotomes cut or incise the in-stent hyperplastic tissue during initial balloon inflation and thus facilitate plaque dilation when the balloon is fully inflated. Previous observational and randomized studies comparing PTCA vs CB for the treatment of in-stent restenosis showed conflicting results regarding the angiographic and clinical out-

comes as well as the mechanism of action of the device, probably due to the different patient characteristics, type of in-stent restenosis and procedural protocols[7-14].

Therefore, the aim of this randomized study was 3-fold: 1) to compare the acute and 24-hour angiographic and intravascular ultrasound (IVUS) changes of PTCA and CB treatment in in-stent restenosis; 2) to investigate the mechanism by which CB and PTCA enlarge the coronary lumen in patients with in-stent restenosis; and 3) to correlate the acute and 24-hour results to clinical follow-up.

Methods

Fifty consecutive patients with angiographic significant in-stent restenosis (> 50% diameter stenosis) were randomized to treatment with conventional PTCA (n = 25) or CB (n = 25). The vast majority of patients in both groups had focal in-stent restenosis and underwent re-angiography for clinical reasons. The remaining patients were asymptomatic with unreliable tests for myocardial ischemia. They were submitted to repeat angiography performed as part of protocols evaluating the long-term patency of new stents. The patients' clinical characteristics are reported in table I.

Study protocol. Having diagnosed significant in-stent restenosis[15], patients were randomized to PTCA or CB treatment. Each patient underwent quantitative coronary angiography (QCA) and IVUS evaluations at baseline, after treatment and at 24 hours. At that time, if a "suboptimal result" was documented (i.e. ≥ 50% diameter stenosis by visual estimate or a minimal lumen area [MLA] ≤ 4.7 mm^2 at IVUS[16]), patients were re-randomized to additional percutaneous treatment (CB for PTCA group and vice versa) or no additional treatment. After hospital discharge, all patients were followed up clinically and underwent exercise stress testing or thallium-201 myocardial scintigraphy performed at 6 months. Re-angiography was carried out in case of symptom recurrence, a positive exercise stress test in patients with single vessel disease or positive thallium-201 myocardial scintigraphy in the stented vessel area in patients with multivessel disease.

Table I. Patient characteristics.

	PTCA (n=25)	CB (n=25)
Mean age (years)	61 ± 10	66 ± 10
Male gender	19 (76%)	17 (68%)
Time from stent implant (months)	8.6 ± 1.9	7.6 ± 1.4
Stent length (mm)	18.9 ± 8.4	19.1 ± 7.6
Target vessel (n=)		
Left anterior descending artery	11 (44%)	14 (56%)
Left circumflex artery	6 (24%)	3 (12%)
Right coronary artery	8 (32%)	8 (32%)
Type of angiographic restenosis (n=)		
Focal	20 (80%)	20 (80%)
Diffuse	5 (20%)	5 (20%)
Reasons for re-angiography (n=)		
Symptoms/signs of ischemia	19 (76%)	18 (72%)
Routine follow-up	6 (24%)	7 (28%)

Differences between groups were not significant. CB = cutting balloon; PTCA = percutaneous transluminal coronary angioplasty.

Procedural protocol. The device size was selected according to an IVUS 1:1 device-to-stent ratio at the level of the MLA. Balloon lengths of 15 or 16 mm and of 10 or 15 mm were used for the PTCA and CB groups respectively. Balloon inflation (multiple if required) was maintained for 60-90 s with a maximal inflation pressure of 8 atm in both groups until < 30% residual angiographic stenosis was achieved. Standard pharmacological treatment (i.v. heparin to achieve an activated clotting time level > 300 s, aspirin 500 mg i.v., i.v. nitrates) was administered to each patient during the procedure. No glycoprotein IIb/IIIa inhibitors were used.

The local ethical committee approved the study protocol and each patient gave written informed consent.

Quantitative coronary angiography analysis. Off-line QCA analysis was carried out by two experienced observers using the ARTREK Quantum IC (Image Comm System, Inc., Sunnyvale, CA, USA). The outer diameter of the contrast-filled catheter was used for calibration. The lesions were analyzed in multiple projections and the reference vessel diameter, minimal lumen diameter, percent diameter stenosis and lesion length ("shoulder to shoulder") were measured from the "worst" angiographic view. Angiographic restenosis was defined as a diameter stenosis > 50%. The in-stent restenosis angiographic pattern was defined, in accordance with a previous report[15], as focal (≤ 10 mm in length, positioned at the body of the stent, the proximal or distal margin or a combination of these sites), extensive intrastent or proliferative (> 10 mm in length and confined to the stent or extending beyond the margins of the stent), or occlusive (occluded vessel with a TIMI flow 0 grade). We defined as multifocal a multiple in-stent restenosis, each ≤ 10 mm in length, separated by at least 10 mm of an apparently normal stented vessel.

Intravascular ultrasound recording and analysis. IVUS imaging was carried out using a 40 MHz mechanical ultrasound transducer rotating at 1800 rpm and withdrawn automatically at 0.5 mm/s within a 3.2F short monorail imaging catheter (CardioVascular Imaging System, Inc., Sunnyvale, CA, USA). Images were recorded on 0.5" high-resolution s-VHS tapes. IVUS imaging was performed after administration of 0.2 mg intracoronary nitroglycerin by advancing the IVUS catheter approximately 10 mm beyond the stent

and performing an automated pullback to the aorto-ostial junction. Off-line IVUS analysis was carried out by two independent observers who were unaware of which study phase they were viewing. In case of a difference between measurements greater than mean ± 2 SD of our cath lab series[14], a third measurement was carried out by the two observers together. The IVUS external elastic membrane area (EEMA), stent area (SA) and MLA were measured (Tape Measure, Indec System, Mountain View, CA, USA) at the level of the intrastent MLA. The reference vessel area was also measured. The in-stent restenosis area (RA) was calculated as SA minus MLA. The plaque area external to the stent – i.e. the original plaque + media area (P+MA) – was calculated as EEMA minus SA. Because acoustic shadowing by target lesion calcium renders measurement of the EEMA difficult, in-stent restenoses containing > 30° of circumferential calcium or > 1.0 mm of axial calcium were excluded. The circumferential arc of calcium was measured using a protractor centered on the lumen; the axial length of calcium was measured by counting the number of seconds of videotape on which lesion calcium was present (2 s of videotape = 1 mm of axial arterial length)[17]. In order to ensure that repeat IVUS measurements were taken always at the same site, we calculated the distance, in frame number, between the first visible distal struts of the stent and the MLA site. This number was kept constant in all IVUS evaluation runs. The reproducibility of this type of IVUS measurement has been reported[18]. Measurements of automated transducer pullback length have been validated[19]. Volumetric IVUS analysis was carried out over a vessel length of 20 mm centered on the pre-intervention in-stent MLA. The same IVUS parameters and related calculations selected for IVUS planar analysis were taken for each slice and used to calculate the following volumes according to Simpson's rule: mean lumen volume (MLV), stent volume (SV), external elastic membrane volume (EEMV) and restenosis volume (RV). Moreover, the length of in-stent restenosis was defined as the axial length in which > 75% of in-stent tissue area reduction was detected.

Statistical analysis. Statistical analysis was carried out with ANOVA analysis for repeated measurements. *Post-hoc*, post-intervention and delayed measurements were compared using the paired Student's t-test with the Bonferroni correction for multiple comparisons. A p value < 0.05 was considered as statistically significant except for *post-hoc* comparisons in which a p value < 0.016 was required (0.05 divided by 3)[20]. The Fisher's exact test was used to compare frequencies.

Results

The patients' clinical and angiographic characteristics at baseline are reported in tables I through III. Acute procedural success was achieved in all patients. One CB patient, with an optimal angiographic and IVUS result at 24 hours, died suddenly 1 day later.

Procedural results. The mean device size, length, number and duration of inflations were: 3.5 ± 0.5 vs 3.4 ± 0.4 mm (p = NS); 15 ± 3 vs 11 ± 2 mm (p = 0.000); 3.8 ± 2.3 vs 3 ± 1 (p = NS) and 167 ± 67 vs 199 ± 87 s (p = NS) for PTCA and CB respectively. The maximal inflation pressure was 8 atm in both groups.

Table II. Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) results in the percutaneous transluminal coronary angioplasty (PTCA) group (n = 25).

	Baseline	PTCA	24 hours
QCA			
RVD (mm)	3.19 ± 0.33	3.20 ± 0.26	3.22 ± 0.29
MLD (mm)	1.07 ± 0.35	2.26 ± 0.41***	2.01 ± 0.42§§
DS (%)	66 ± 10	29 ± 12***	37 ± 13§§
IVUS			
MLA (mm^2)	2.54 ± 1.0	7.36 ± 1.9***	5.45 ± 1.38§§†
SA (mm^2)	9.75 ± 2.4	10.7 ± 2.7	10.6 ± 2.6
EEMA (mm^2)	18.1 ± 5.3	18.9 ± 5.2	19.1 ± 5.3
RA (mm^2)	7.2 ± 2.0	3.4 ± 1.4**	5.1 ± 2.3§††
P+MA (mm^2)	8.4 ± 3.8	8.2 ± 3.3	8.6 ± 3.4
MLV (mm^3)	108 ± 30	148 ± 33***	131 ± 28§§
SV (mm^3)	151 ± 34	165 ± 37	165 ± 36
EEMV (mm^3)	316 ± 74	336 ± 80	325 ± 85
RV (mm^3)	92 ± 21	72 ± 22*	88 ± 29
P+MV (mm^3)	131 ± 40	128 ± 43	129 ± 44

Results are expressed as mean ± SD. DS = diameter stenosis; EEMA = external elastic membrane area; EEMV = external elastic membrane volume; MLA = minimal lumen area; MLD = minimal lumen diameter; MLV = minimal lumen volume; P+MA = plaque + media area; P+MV = plaque + media volume; RA = restenosis area; RV = restenosis volume; RVD = reference vessel diameter; SA = stent area; SV = stent volume. Post-hoc analysis: * p = 0.01, ** p = 0.003, *** p = 0.000 baseline vs PTCA; § p = 0.003, §§ p = 0.000 baseline vs 24 hours; † p = 0.01, †† p = 0.001 PTCA vs 24 hours.

Table III. Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) results in the cutting balloon (CB) group (n = 25).

	Baseline	CB	24 hours
QCA			
RVD (mm)	3.28 ± 0.53	3.26 ± 0.49	3.21 ± 0.47
MLD (mm)	0.93 ± 0.38	2.31 ± 0.38*	2.25 ± 0.30**
DS (%)	68 ± 11	23 ± 11*	26 ± 11**
IVUS			
MLA (mm^2)	1.81 ± 0.7	7.3 ± 2.1*	6.9 ± 2**
SA (mm^2)	9.4 ± 2.9	10.6 ± 3	10.6 ± 3.1
EEMA (mm^2)	16.3 ± 5.3	17.6 ± 5.3	17.9 ± 5.6
RA (mm^2)	7.5 ± 3.0	3.3 ± 1.5*	3.7 ± 1.7**
P+MA (mm^2)	6.9 ± 2.8	7.0 ± 2.7	7.3 ± 2.8
MLV (mm^3)	90 ± 29	129 ± 29*	129 ± 30**
SV (mm^3)	125 ± 38	136 ± 34	134 ± 35
EEMV (mm^3)	288 ± 95	304 ± 83	311 ± 85
RV (mm^3)	104 ± 43	83 ± 38	84 ± 40
P+MV (mm^3)	99 ± 30	93 ± 25	98 ± 26

Results are expressed as mean ± SD. DS = diameter stenosis; EEMA = external elastic membrane area; EEMV = external elastic membrane volume; MLA = minimal lumen area; MLD = minimal lumen diameter; MLV = minimal lumen volume; P+MA = plaque + media area; P+MV = plaque + media volume; RA = restenosis area; RV = restenosis volume; RVD = reference vessel diameter; SA = stent area; SV = stent volume. Post-hoc analysis: * p = 0.000 baseline vs CB; ** p = 0.000 baseline vs 24 hours.

Quantitative coronary angiography and intravascular ultrasound results (Tables II to IV). At baseline, PTCA patients had a significantly greater MLA (2.54 ± 1.0 vs 1.81 ± 0.7 mm^2, p < 0.004), MLV (108 ± 30 vs 90 ± 29 mm^3, p = 0.04), SV (151 ± 34 vs 125 ± 38 mm^3, p = 0.05) and P+MV (131 ± 40 vs 99 ± 30 mm^3, p = 0.003) than CB patients. After intervention, MLA and MLV significantly increased and RA and RV decreased in both groups. No significant change was observed in SA and SV, EEMA and EEMV and P+MA and P+MV (Tables II and III). There was no difference in the delta changes in both groups (Table IV). Post-intervention, MLA was significantly smaller (p = 0.001) than pre-intervention SA (reflecting the lumen area immediately after stenting) in both groups.

At the 24-hour control, MLA significantly decreased and RA significantly increased in the PTCA group only. The delta changes of these two variables were significantly greater for PTCA than for CB (MLA: -1.9 ± 1.4 vs 0.37 ± 0.8 mm^2, p = 0.000; RA:

Table IV. Delta changes in quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) parameters after intervention and at 24 hours in the percutaneous transluminal coronary angioplasty (PTCA) and cutting balloon (CB) groups.

	Baseline vs intervention		Intervention vs 24 hours	
	PTCA	CB	PTCA	CB
QCA				
RVD (mm)	0.02 ± 0.23	-0.02 ± 0.21	0.03 ± 0.2	-0.07 ± 0.2
MLD (mm)	1.19 ± 0.44	1.37 ± 0.55	-0.23 ± 0.34	-0.06 ± 0.23§
DS (%)	-37 ± 14	-45 ± 13*	7.7 ± 10	2.8 ± 7
IVUS				
MLA (mm^2)	4.81 ± 1.9	5.45 ± 2.0	-1.9 ± 1.4	0.37 ± 0.8§§
SA (mm^2)	0.92 ± 1.0	1.21 ± 1.1	0.8 ± 0.8	1.2 ± 0.7
EEMA (mm^2)	0.8 ± 1.1	1.3 ± 1.4	0.20 ± 1.0	0.25 ± 0.86
RA (mm^2)	-3.8 ± 1.3	-4.2 ± 1.7	1.74 ± 1.3	0.37 ± 0.52§§
P+MA (mm^2)	0.21 ± 1.1	0.06 ± 1.4	-0.37 ± 0.9	-0.25 ± 1.1
MLV (mm^3)	40 ± 15	39 ± 17	-17 ± 15	-0.25 ± 8§§
SV (mm^3)	14 ± 7	15 ± 11	-0.06 ± 7	-2 ± 5
EEMV (mm^3)	20 ± 18	16 ± 26	-1.1 ± 21	6 ± 9
RV (mm^3)	-20 ± 12	-22 ± 16	16 ± 12	1 ± 6§§
P+MV (mm^3)	-3 ± 12	-6 ± 12	0.7 ± 8	5 ± 5

Results are expressed as mean ± SD. DS = diameter stenosis; EEMA = external elastic membrane area; EEMV = external elastic membrane volume; MLA = minimal lumen area; MLD = minimal lumen diameter; MLV = minimal lumen volume; P+MA = plaque + media area; P+MV = plaque + media volume; RA = restenosis area; RV = restenosis volume; RVD = reference vessel diameter; SA = stent area; SV = stent volume. * p = 0.03 baseline vs intervention; § p = 0.03, §§ p = 0.000 intervention vs 24 hours.

1.74 ± 1.3 vs 0.37 ± 0.52 mm^2, p = 0.000). Volumetric analysis paralleled planar analysis showing a significant MLV loss (-17 ± 15 vs -0.25 ± 8 mm^3, p = 0.000) and RV increase (16 ± 12 vs 1 ± 6 mm^3, p = 0.000).

A "suboptimal result" was found in 10 patients. Six had a MLA ≤ 4.7 mm^2 only, 3 had both a MLA ≤ 4.7 mm^2 and a percent diameter stenosis ≥ 50%, and 1 showed a percent diameter stenosis ≥ 50% only. The mean percent diameter stenosis and MLA were 40 ± 11% and 4.1 ± 0.77 mm^2 respectively. The mean lumen area loss was 1.9 ± 1.5 mm^2 (-28 ± 17%). "Instant restenosis" was diagnosed in these patients. This finding was more frequently found in the PTCA than in the CB group (9 [36%] vs 1 [4%], p < 0.01). Figures 1 and 2 show an example of acute and 24-hour result in the PTCA and CB groups.

Long-term follow-up. The results of follow-up are reported in table V. During a mean follow-up of 6 ± 1 months, 5 additional patients of the PTCA group and 3 patients of the CB group had target lesion revascularization (Fig. 3). The cumulative target lesion revascularization (24 hours + follow-up) was significantly

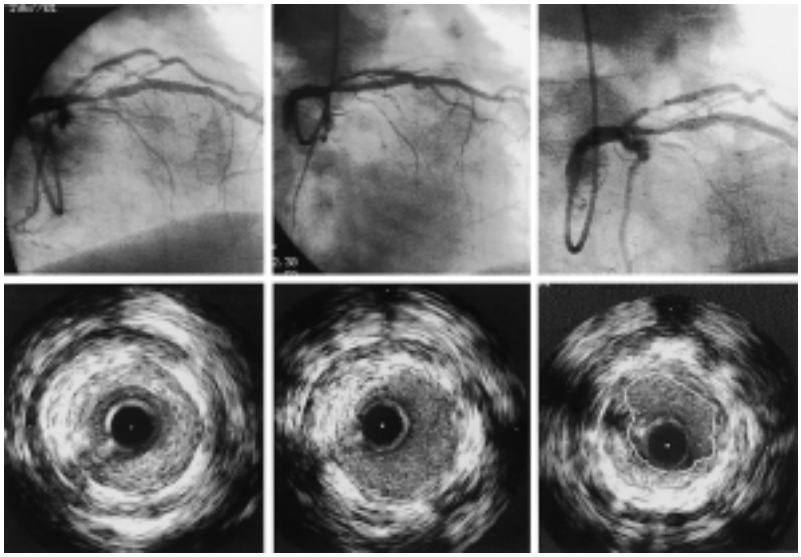

Figure 1. *Angiographic and intravascular ultrasound images of the proximal left anterior descending coronary artery in-stent restenosis at baseline* (left panel)*, after percutaneous transluminal coronary angioplasty* (middle panel) *and at 24 hours* (right panel). *The acute angiographic and intravascular ultrasound results showed optimal lumen dilation. The 24-hour control showed "instant restenosis" (quantitative coronary angiography diameter stenosis > 50% and intravascular ultrasound minimal lumen area of 4.5 mm^2 [white contour]).*

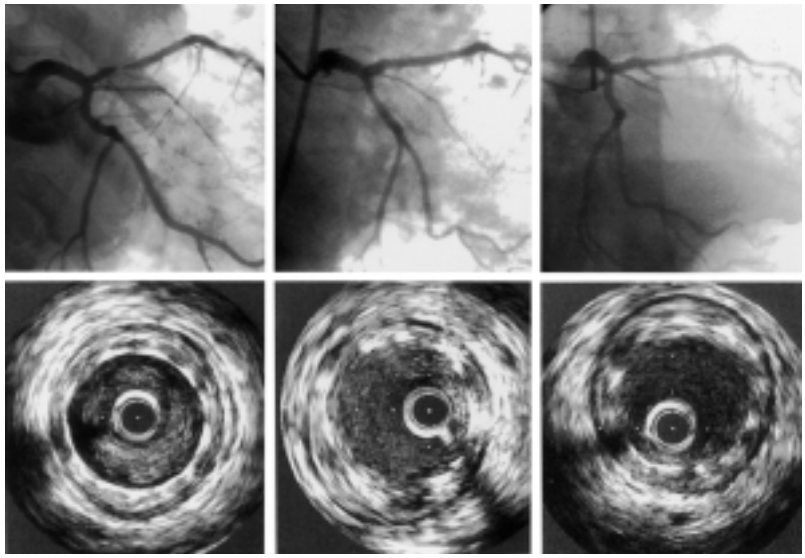

Figure 2. *Angiographic and intravascular ultrasound images of the proximal left anterior descending coronary artery in-stent restenosis at baseline* (left panel)*, after cutting balloon* (middle panel) *and at 24 hours* (right panel). *The angiographic and intravascular ultrasound results were optimal both immediately after the procedure and 24 hours later.*

Table V. Follow-up (8-180 days).

	PTCA (n=25)	CB (n=24)	p
Mortality	0/25	0/24	NS
Asymptomatic	18/25 (72%)	21/24 (87%)	NS
Negative EST/MS	16/25 (64%)	18/24 (75%)	NS
MACE*	7/25 (28%)	4/24 (17%)	NS
Instant restenosis	9/25 (36%)	1/25 (4%)	< 0.01
TLR			
Acute (1-7 days)**	5/9	0/1	
Long-term (8-180 days)	5/25 (20%)	3/24 (12.5%)	NS
Cumulative (1-180 days)	10/25 (40%)	3/25 (12.5%)	< 0.05
PCI on other vessels	2/25 (8%)	1/24 (4%)	NS
Event-free survival	18/25 (72%)	20/24 (83%)	NS

CB = cutting balloon; EST = exercise stress test; MACE = major adverse cardiac events; MS = myocardial scintigraphy; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; TLR = target lesion revascularization. * death, Q/non-Q wave myocardial infarction, re-PTCA or coronary artery bypass surgery; ** according to randomization.

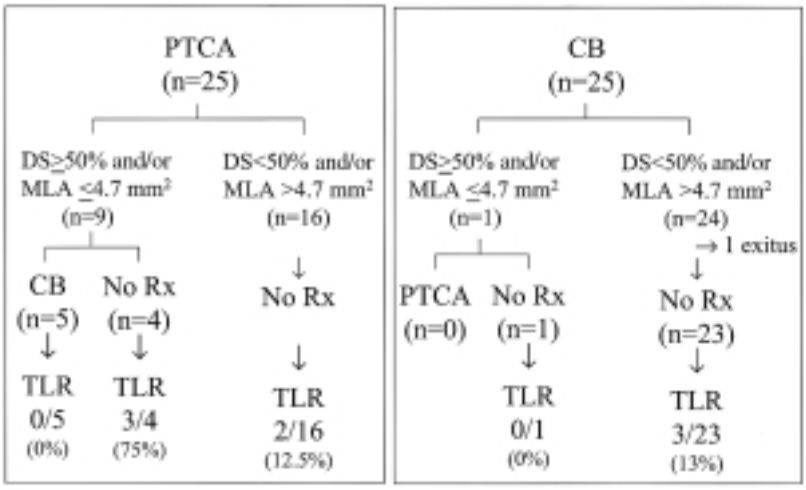

Figure 3. *Long-term target lesion revascularization (TLR) rate after the second randomization in the percutaneous transluminal coronary angioplasty (PTCA) and cutting balloon (CB) group patients. DS = diameter stenosis; MLA = minimal lumen area; Rx = treatment.*

greater for PTCA than for CB (10/25 [40%] vs 3/25 [12.5%], $p < 0.05$). The relative risk of having target lesion revascularization for each procedure in the PTCA group was 1.5 (95% confidence interval 1.06-2.1).

Discussion

The mechanism of lumen enlargement by PTCA and/or CB in in-stent restenosis is probably due to many factors. First of all, the method used to select the device size (i.e. visual inspection, QCA, IVUS). Secondly, the balloon-to-artery or balloon-to-stent ratio and device inflation pressure. Finally, the pre-treatment stent lumen area and type of peristent plaque. The combination of these variables may lead to several types of response and probably accounts for the different results reported in the literature. Thus, methodological and procedural variables as well as anatomic characteristics should be adequately matched to investigate the mechanism of action and compare the effects of different devices. In our patient population, the size of the two devices was selected by IVUS according to a 1:1 device-to-stent ratio. The balloon inflation pressure was nominal in all cases. This procedural approach was intended to achieve an effective lumen dilation (even with low inflation pressure in the PTCA group) while limiting any additional stent expansion (a known independent predictor of restenosis[21]) and to specifically investigate the effect of both devices on hyperplastic tissue. A potential risk of using such as "conservative" approach is to leave an under-expanded stent (a 30-40% occurrence[22]) untreated. However, the baseline SA was quite large in both groups with the majority of patients having a value > 7.5 mm^2 or > 80% of the distal reference vessel area, suggesting an optimal stent deployment during the initial procedure.

The present study. This study provides many interesting results: 1) both PTCA and CB effectively, and to the same extent, enlarge the coronary artery lumen in in-stent restenosis; 2) the mechanism by which both devices dilate the vessel lumen includes in-stent tissue reduction (i.e. redistribution) and mild, additional stent dilation; 3) at 24 hours, a significantly greater loss of acute lumen gain occurs in PTCA than in CB (the "instant restenosis" phenomenon); 4) the long-term target lesion revascularization is significantly lower in the CB than in the PTCA group.

Acute results and mechanism of action of lumen enlargement. The coronary lumen was effectively enlarged by PTCA and CB in all patients. There was no difference in the delta changes for any QCA or IVUS parameter between the two groups. The SA slightly increased by 9 and 12% in PTCA and CB respectively. Of the total mean lumen area increase, 77 and 79% were the result of in-stent tissue reduction and 23 and 21% were the result of further stent dilation in both groups respectively. These results are somewhat different from those reported in previous studies evaluating the effects of PTCA in in-stent restenosis. In these studies, the SA increase ranged from 21 to 33% accounting for 45% of the total lumen enlargement, while the RA decrease accounted for the remaining 55%[23-26]. These differences with respect to our study are largely explained by methodological factors: the method used to select the device size (visual estimate or QCA vs IVUS), the inflation pressure (high vs low), and the pre-treatment SA.

Following intervention, there was no significant change in P+MA and P+MV in both groups. This suggests that the reduction of in-stent tissue was mainly due to radial and longitudinal redistribution (within a larger SA) rather than to extrusion of the material out of the stent struts as previously suggested[23-26]. The volumetric analysis supports this interpretation showing a paradoxical reduction in the lumen cross-sectional area and an increase in P+MA outside the stent edges (Fig. 4). Although IVUS cannot differentiate between the reference vessel lumen reduction due to in-stent tissue or peristent plaque redistribution, the unchanged P+MA and P+MV throughout the stent length is in favor of this hypothesis. Besides, peristent fibrous changes taking place over time following stent implantation would make tissue extrusion out of the stent struts difficult[23]. Similar plaque displacement has been found to be a primary mechanism of lumen enlargement following PTCA of both non-stented and stented lesions[27,28].

Twenty-four-hour quantitative coronary angiography and intravascular ultrasound results. The acute results were maintained at the 24-hour evaluation in the CB group whereas the PTCA group showed a significantly greater loss in MLA and MLV and an increase in RA and RV. This phenomenon, termed "instant restenosis", has been shown to occur soon after successful treatment of in-stent restenosis and has been attributed to tissue reintrusion through the stent struts and to some degree to stent recoil[25]. However, in our study, SA and SV and P+MA and P+MV did not significantly change over time, suggesting that the lumen loss was mainly the result of in-stent tissue collapse. Which degree of tissue collapse should be considered clinically signifi-

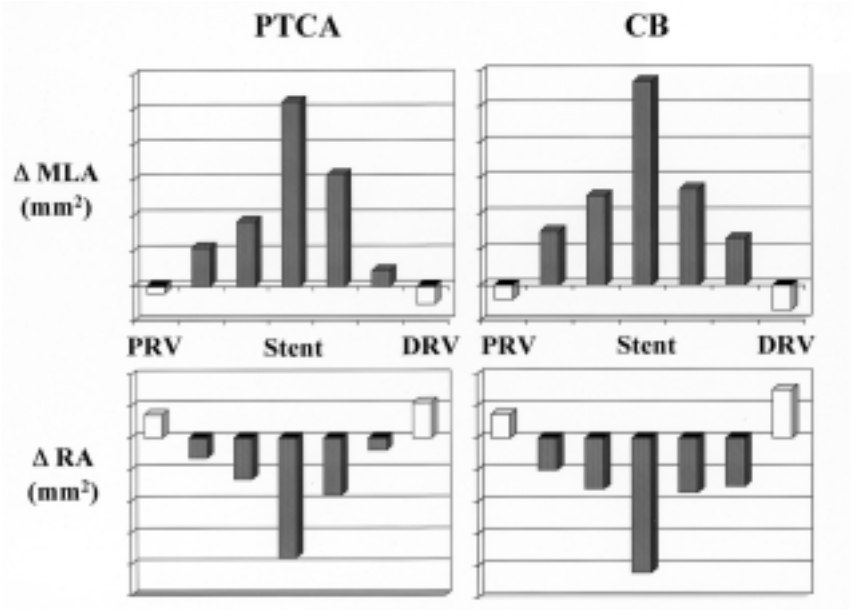

Figure 4. *Absolute changes (mm²) in the minimal lumen area (MLA) and restenosis area (RA) following percutaneous transluminal coronary angioplasty (PTCA) and cutting balloon (CB) at 5 intrastent sites* (gray columns) *and at 2 sites out of the stent edges* (white columns). *The maximal increase in MLA and decrease in RA occur at the center of the lesion. Out of the stent edges a paradoxical reduction in MLA and increase in RA are shown in both groups. DRV = distal reference vessel; PRV = proximal reference vessel.*

cant is still unsettled. Schiele et al.[16] found an IVUS MLA ≤ 4.7 mm^2 after percutaneous re-intervention for in-stent restenosis as the only independent predictor of a negative long-term clinical outcome. Using single or combined angiographic and IVUS cut-offs (i.e. ≥ 50% diameter stenosis and/or IVUS MLA ≤ 4.7 mm^2) to define significant instant restenosis, we were able to identify 10 out of 50 (20%) patients who fulfilled these criteria. This pattern was more frequently detected at IVUS (90%) than at angiography (40%) and more frequently occurred in PTCA than in CB patients (36 vs 4%, $p < 0.01$). This suggests a more stable and uniform in-stent tissue dilation and redistribution following CB probably due to its peculiar design and mechanism of dilation.

Long-term follow-up. At a mean follow-up of 6 months, the target lesion revascularization was significantly lower in the CB than in the PTCA group (12 vs 40%, $p < 0.05$). In the PTCA group, the number of target lesion revascularizations included the 5 patients with "instant restenosis" who were randomized to additional percutaneous treatment plus 5 other patients who became symptomatic late during follow-up (Fig. 4). We do not know whether patients randomized to a second treatment because of a suboptimal result at 24 hours would ever have required target lesion revascularization. However, among the 4 patients who were randomized to no additional treatment, 3 (75%) required target lesion revascularization, confirming the role of "instant restenosis" as a predictor of late events. Interestingly, in patients without "instant restenosis" after treatment with both devices the rate of late target lesion revascularization was similarly low (Fig. 4). This would suggest that if significant early lumen loss is avoided, late target lesion revascularization is mainly caused by the in-stent tissue hyperplastic response. If this holds true, a "conservative" protocol aimed at limiting vessel wall trauma appears to be a rational approach. Thus, the long-term outcome of percutaneous treatment for in-stent restenosis is the result of an acute device-related effect and late procedural-related response.

Limitations of the study. Several limitations need to be addressed. Firstly, the study population was small and consisted mainly of focal in-stent restenosis in relatively large vessels with well-expanded stents. We do not know whether these results may be extrapolated to other in-stent restenosis subsets. Secondly, the effects of high inflation pressures (> 12 atm) were not evaluated in the PTCA group. Although the use of high pressure is common practice in the treatment of in-stent restenosis with PTCA, there are no randomized studies showing better acute and long-term clinical and angiographic outcomes by using inflation pressures > 12 or < 12 atm. Schiele et al.[24] showed no additional lumen enlargement following high pressure vs low pressure PTCA for in-stent restenosis, while the stent was further over-expanded with high pressure resulting in a potential trigger of a greater hyperplastic response. In our study, the use, for the first time, of IVUS allowed us to select the ideal balloon size in order to maximize the dilation effect and minimize stent overstretching with a low-pressure technique. This approach, as shown by Sakamoto et al.[26], probably results in a larger balloon diameter selection as compared to the conventional method using angiographic parameters. Thirdly, the second randomization was not blind. Finally, the higher target lesion revascularization of the PTCA group could have been influenced by the patients in this group who were given additional treatment with CB.

Conclusions. When guided by the same technique and procedural protocol, PTCA and CB effectively and to the same extent dilate the coronary lumen in in-stent restenosis. The mechanism of action is the same and includes in-stent tissue redistribution and mild additional stent expansion. Significant early lumen loss (instant restenosis) occurs more frequently in PTCA patients and probably plays an important role in determining the long-term outcome.

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