REVIEW

New recipes for in-stent restenosis: cut, grate, roast, or sandwich the neointima?

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Accepted 19 July 2000

In-stent restenosis is set to become a large part of our interventional practice in the new millennium. Stent implantation has grown so much that it now comprises 60–70% of all percutaneous coronary revascularisation interventions, and assuming a conservative 25% restenosis rate for a total of around one million percutaneous transluminal coronary angioplasty (PTCA) procedures this year, more than 150 000 lesions will need treatment because of in-stent restenosis. The increasing popularity of stent implantation is because of improvements in immediate gain, in tackling dissections, in preventing recoil after PTCA, and in reducing late restenoses, which have been documented in many randomised trials where results have been compared with PTCA. However, despite excellent immediate results, stents have not eliminated restenosis, especially in complex lesions with diffuse coronary disease or in small vessels.^{1–4} Furthermore, the mechanism of in-stent restenosis is very different from that of restenosis after conventional percutaneous treatment (PTCA, directional, rotational, or laser atherectomy). Lumen narrowing after these latter interventions is mainly caused by late wall recoil, and this negative remodelling of the treated segment can easily be treated with a new PTCA or by stent implantation.^{5–6} The stent, on the other hand, maintains the expansion it reaches after the procedure and all the reduction in lumen diameter is caused by intimal hyperplasia.⁷ The challenge to the interventionist in the coming years is how to prevent and treat this condition. Recently the Washington group suggested an angiographic classification of in-stent restenosis according to lesion length and geographical distribution of intimal hyperplasia in relation to the implanted stent. Four patterns of in-stent restenosis were suggested (table 1), with different impacts on the late outcome after a new revascularisation procedure.⁸

Balloon angioplasty

Repeat balloon angioplasty for in-stent restenosis is an easy and safe procedure with a high procedural success.⁹ The initial experiences, however, were limited to lesions treated with a single Palmaz–Schatz stent in rather large vessels, and most of the restenoses were focal.^{10–12} The expansion of the indications for stent implantation and the use of long stents have dramatically increased the incidence of the “malignant” types of in-stent restenosis (diffuse, proliferative, and totally occlusive), reported to account for 58% of all restenoses.⁸

The recurrence of restenosis after repeat angioplasty for the treatment of in-stent restenosis is influenced by its pattern.^{8 13–14 15–20} Reimers and colleagues found that the length of restenosis was associated with a higher risk of new target lesion revascularisation.¹³ Eltchaninoff and associates observed a recurrent restenosis rate of 31% for focal in-stent restenosis and 63% for diffuse in-stent restenosis.¹⁵ A prohibitive recurrence rate of 83% has been reported for total occlusions after stent placement treated with PTCA.²¹

These results can be explained by the mechanism of action of PTCA for in-stent restenosis, well documented with intravascular ultrasound (IVUS) studies before and after treatment. The lumen enlargement after balloon angioplasty is the combined effect of further stent expansion and extrusion–axial redistribution of the neointima. Of the total lumen enlargement, 56% is attributable to additional stent expansion while 44% is the result of an apparent decrease (displacement) in neointimal tissue.²² In addition, there is significant tissue reintrusion shortly after catheter based treatment of in-stent restenosis, which results in early lumen loss.²³ So, at least for lesions with inadequate initial expansion of the stent and for very focal neointimal growths, balloon dilatation can be an effective solution, both immediately and in the long term.^{19 20} PTCA treatment of diffuse hyperplastic reactions within well expanded stents achieves suboptimal immediate results and has a poor long term outcome.^{15 16} Different techniques have been proposed, with an interesting feature in common—they have all been used in the treatment of de novo lesions without any

Table 1 Angiographic patterns of in-stent restenosis (ISR)

	Pattern of ISR	Length	Geographical distribution
Class I	Focal	≤ 10 mm	Body of the stent, proximal or distal margin (but not both), combination of these sites (multifocal)
Class II	Diffuse intrastent	> 10 mm	Confined to the stent without extending outside the margins
Class III	Diffuse proliferative	> 10 mm	Extended beyond the margin(s) of the stent
Class IV	Total occlusion	–	TIMI flow 0

Figure 1 Limitations of rotational atherectomy in treatment of in-stent restenosis.

clear advantage over PTCA, and they have now generated a surge of new interest for their use in the treatment of diffuse in-stent restenosis.

Cutting balloon angioplasty

The cutting balloon is a standard monorail or over-the-wire balloon catheter with three to four microblades of 0.18 mm depth and 0.70–0.76 mm thickness, which are longitudinally attached to the balloon and folded within the balloon before treatment. When the balloon is inflated, the cutting blades are exposed. As inflation continues and the balloon expands, the blades surgically incise the restenotic plaques up to the metallic stent cage. These incisions should then facilitate the maximum extrusion of the neointimal plaque, separated into three or four quadrants. The cutting balloon also has a practical advantage over a traditional PTCA balloon for treatment of in-stent restenosis: traditional PTCA balloons, and especially short balloons, when positioned within restenotic lesions tend to move forward or backward during inflation into larger segments with lower resistance, because the hyperplastic tissue has a smooth slippery surface. With a cutting balloon this problem is prevented by the blades, which anchor the balloon to the plaque during balloon inflation. The treatment can be performed with cutting balloons of optimal length (10 mm), with a lower risk of dissection at the stent margins.

Cutting balloon angioplasty for in-stent restenosis is associated with lower restenosis and target lesion revascularisation rates (7.7% to 29% and 3.8% to 22%, respectively).^{24–26}

In a comparative retrospective analysis conducted at the Columbus Clinic and San Raffaele Hospital, 242 in-stent restenotic lesions were treated with cutting balloon, conventional PTCA, and rotational atherectomy.²⁷ At a six month follow up, recurrence of angiographic restenosis occurred in 25% of the cutting balloon group, 43% of the conventional PTCA group, and 34% of the Rotablator group ($p < 0.001$), with target lesion revascularisation (TLR) values of 18%, 29% and 27%, respectively (NS). Observations with intravascular ultrasound suggest that the incisions created on the plaque by the microblades facilitate maximum dilatation of the balloon and maximum plaque extrusion out of the stent compared with a traditional PTCA balloon. A recent IVUS study²⁸ has shown that immediately after cutting balloon angioplasty the lumen cross sectional area was greater than after traditional PTCA (mean (SD), 4.0 (1.7) mm² v 3.3 (0.7) mm², $p < 0.05$), and this difference was maintained at the six month follow up (3.9 (2.2) mm² v 3.4 (3.1) mm²).

Atheroablation

Rotational atherectomy, excimer laser atherectomy, directional atherectomy, and pull back atherectomy can be used to remove neointima after stent implantation. Serial ultrasound

studies have been conducted with rotational and laser atherectomy, showing that both devices can remove neointima.²⁹⁻³⁰ A quantitative angiographic study conducted in a larger patient population has confirmed that the final maximum lumen diameter achieved after rotational atherectomy with adjunctive PTCA is larger than after PTCA alone.³¹ Single centre studies or multicentre registries of rotational atherectomy in the setting of diffuse in-stent restenosis have suggested a lower incidence of restenosis compared with PTCA.³²⁻³⁸ The preliminary report of the final results of the first randomised trial comparing aggressive rotablation and balloon angioplasty (ARTIST, angioplasty versus rotablation for treatment of in-stent stenosis) has been more disappointing, with a restenosis rate after rotablator of 70% compared with 51% after conventional PTCA ($p = 0.04$).³⁷ As the preliminary results of a randomised trial in the USA (the ROSTER (rotablator versus balloon for stent restenosis)

study³⁹) were opposite to this, the efficacy of rotational atherectomy remains controversial, although such high rates of restenosis suggest that these technically cumbersome, time consuming, and expensive methods do not offer a final solution to the problem of in-stent restenosis.

When one considers, however, the percentage of neointima actually removed, even with the largest rotablator burrs, the commonly used definition of “debulking” technique appears ridiculous. As shown in fig 1, even assuming the creation of a neolumen exactly matching the burr size, the “bulk” of the lesion will still be there when a 2.5 mm rotablator is passed through a diffuse restenosis in a stent previously expanded to 3.5 or 4.0 mm.

The claim that eccentric laser catheters and homogeneous light distribution can improve efficiency still has to be proven in the clinical setting.²⁹⁻³⁹⁻⁴¹ Other atherectomy catheters (pull back atherectomy, X-Sizer X-Tract) cannot dig

Table 2 Clinical studies on in-stent restenosis

Author	Year	Number of lesions	Type of study	Device	Lesion length (mm)‡	Angio follow up (%)	Restenosis rate	Clinical follow up (months)‡	TLR (%)	Notes
Baim <i>et al</i> ¹⁰	1993	105	Reg	PTCA	—	47.6	54	7.0 (6.3)	30	
Gordon <i>et al</i> ¹¹	1993	30	Reg	PTCA	—	46.6	57	6.8 (4.6)	—	
Schoemig <i>et al</i> ¹²	1994	31	Reg	PTCA	18.6 (9.4)	84	38.5	5.2 (2.4)	—	
Macander <i>et al</i> ⁶	1994	75	Reg	PTCA	—	38	30	5.4 (3.4)	26	
Reimers <i>et al</i> ¹³	1997	127	Reg	PTCA	12.5 (7.5)	—	—	27.4 (14.7)	11	Focal lesions 62%; stents (13), RA (4), ELCA (2)
Bauters <i>et al</i> ¹⁴	1998	107	Reg	PTCA	—	85	22	6.3 (2.1)	17	Focal disease 71%; stents (14 lesions, 13%)
Eltchaninoff <i>et al</i> ¹⁵	1998	52	Reg	PTCA	16 (8)	92	54	5.3 (3.5)	35	Diffuse disease 71%
Bossi <i>et al</i> ¹⁶	1999	262	Reg	PTCA	—	—	—	6	9.4* v 19.4†	
Yokoi <i>et al</i> ¹⁷	1999	320	Reg	PTCA	—	—	51	12	15.2* v 31.8†	Non-elective stenting 11%
Jolly <i>et al</i> ¹⁸	1999	202	Reg	PTCA (155) RA (33) Stent (14)	10.5 (9.2) 13.4 (10.1) 11.2 (10.3)	—	—	8 (median)	22	2nd, 3rd, 4th, 5th, recurrent ISR 68%, 78%, 74%, 92%, respectively TLR with RA 16% v 21% with PTCA ($p = 0.87$)
Mehran <i>et al</i> ²¹	1999	357	Retr match	PTCA v stent	7.3 (2.1) v 8.1 (1.3) (NS)	—	—	12	25 v 27 (NS)	Focal restenosis; more frequent in-hospital non-Q MI in stent group
Wolf <i>et al</i> ²²	1999	225	Reg	PTCA	<5 mm v >5 mm	100	27.9 v 44.3	5.0 (2.9)	27.9 v 39	
Nakamura <i>et al</i> ²⁴	1998	167	Reg	CB	17.2 (10.5)	72	29	4.7 (2.5)	22	
Chevalier <i>et al</i> ²⁵	1999	45	Rand	PTCA v CB	—	—	—	9	20 v 12 (NS)	Diffuse disease
Mizobe <i>et al</i> ²⁶	1999	50	Rand	CB v PTCA	—	100	7.7 v 32 ($p=0.028$)	6	3.8 v 28 ($p=0.047$)	Rerestent lesions after PTCA for in-stent restenosis; IVUS guided CB
Adamian <i>et al</i> ²⁷	1999	242	Retr match	CB RA PTCA	—	70 71 83	25 34 43	6.2 (2.6)	18 27 29	
Goldberg <i>et al</i> , BARASTER Registry ³²	1997	153	Reg	RA	21 (12)	—	—	6 (3)	40	Diffuse disease 85%; stand alone RA 28% (TLR 67% v 42% when adjunctive PTCA was done)
Sharma <i>et al</i> ³³	1998	100	Reg	RA (+adjunct PTCA)	17 (11)	—	—	13 (5)	26	Diffuse disease 81%
Lee <i>et al</i> ³⁴	1998	81	Reg	RA+PTCA PTCA alone	15 (7) 13 (6)	—	—	9.2 (3.6)	0 4.5	Diffuse disease
Noda <i>et al</i> ³⁵	1999	344	Reg	PTCA or RA	—	—	B-1: 36; R-1:42 (NS) B-2:72 R-2:82 (NS)	—	B-1: 25; R-1:23 (NS) B-2:47; R-2:72 (NS)	
Dauermann <i>et al</i> ³⁶	1998	60	Reg	First ISR v second ISR PTCA v RA PTCA v DCA	13.5 (8.3) 18.4 (13.2)	—	—	11 (median)	43 27 (NS)	Diffuse restenosis
Vom Dahl <i>et al</i> ³¹	1999	100	Reg	RA+PTCA	21 (8)	72	49	5 (4)	35	
Radke <i>et al</i> ³⁰	1999	49	Reg	RA+PTCA	22.4 (20.2)	89	45	6.6 (2.5)	38	Diffuse disease
Vom Dahl <i>et al</i> , for ARTIST ³⁷	1999	298	Rand	RA v PTCA	—	—	—	6	70 v 51	Diffuse disease
Sharma <i>et al</i> , for ROSTER ³⁸	1999	150	Rand	RA v PTCA	—	—	—	12 (4)	20 v 43	End point: clinical restenosis

*Focal restenosis.

†Diffuse restenosis.

‡Mean (SD).

Angio, angiographic; CB, cutting balloon angioplasty; ELCA, excimer laser catheter angioplasty; ISR, in-stent restenosis; IVUS, intravascular ultrasound; PTCA, percutaneous transluminal coronary angioplasty; RA, rotational atherectomy; Rand, randomised study; Reg, registry; Retr match, retrospective matched study; TLR, target lesion revascularisation.

holes greater than their physical size or still have to prove their efficacy for the effective removal of neointimal tissue.⁴²⁻⁴⁴

Directional atherectomy is the only true “debulking” technique, as multiple circumferential cuts can effectively remove most of the neointima and restore lumen patency.⁴⁵ The insertion of a big rigid catheter is cumbersome unless straight proximal vessel segments are treated. The activation of the cutter through the stent struts may disrupt stent integrity or create sharp edges that will puncture balloons.⁴⁶ Debulking of restenotic tissue with directional atherectomy in a small series of patients with mostly diffuse in-stent restenosis resulted in a TLR rate of 28% at a mean (SD) follow up of 10 (4.6) months.⁴⁷ Conceptually, removal of neointima is the best method of treating in-stent restenosis but, in order for it to be practical and effective, new low profile flexible atherectomy catheters are required that circumferentially shave the neointima up to the inner surface of the stent strut.

Stent sandwich

The persistence of residual stenosis and of a hazy appearance within the stent after PTCA, as well as the presence of dissections at the stent ends, are common after PTCA or after combined “debulking” and adjunctive PTCA. Deployment of new stents is a quick and effective solution to the problem, restoring the pristine result of the initial stent implantation. The drawbacks, however, are conceptually obvious: a longer segment than the initial stent length is covered with stents, while extreme stretching is imposed on the outer vessel wall and so a new powerful stimulus to hyperplasia is introduced in a patient known to be prone to neointimal proliferation. These theoretical limitations may explain the poor long term results observed with stent implantation for in-stent restenosis.⁴⁸⁻⁵⁸ The only rationale for the elective use of a second stent to treat in-stent restenosis is the presence of severe underexpansion or collapse of the initial stent, not correctable by PTCA. These conditions may occur for coil stents and also for slotted tubular stents implanted in very calcified segments or at ostial locations.

Exclusion of the proliferative neointimal tissue behind PTFE covered stents has also been tried, but restenosis was often observed at the stent edges, possibly because of the incomplete tissue coverage at the extremities of this device.⁵⁸

Future directions

Why do we waste time discussing mechanical interventions for a self perpetuating biological phenomenon which will soon be prevented and treated by the use of radiation therapy? First of all, radiation does not instantaneously melt down the neointima that has already accumulated, which is mainly formed by acellular matrix, and effective lumen patency must be restored before radiation treatment. Secondly, as this is a treatment with long term biological implications that are still to be defined (late vessel shrinkage, carcinogenesis), it is unlikely

to be applied routinely for restenosis prevention and treatment. Brachytherapy also involves a multitude of non-cardiology specialists (physicists, radiation oncologists, technicians, and safety officers). For these reasons, radiotherapy, despite the promising results of recent trials,⁵⁹⁻⁶² is unlikely to surpass mechanical interventions in terms of safety, simplicity, and cost-effectiveness for the initial treatment of in-stent restenosis, and will probably be limited to malignant types of restenosis or patients with multiple recurrences.

It took 15 years after the introduction of PTCA before a device was available—the stent—which could halve the restenosis rate after PTCA in optimal lesion subsets. As is so often the case in medicine and biology, the solution to a problem generates new problems and requires new solutions. The application of old techniques—of limited efficacy in treating de novo lesions—to the management of in-stent restenosis (table 2) is unlikely to solve a new problem which requires creative solutions and the development of new dedicated therapeutic devices.

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