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Review article

The challenge of in-stent restenosis: insights from intravascular ultrasound

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Intravascular ultrasound;
Stent implantation;
IVUS guidance;
Brachytherapy;
Drug-eluting stent

Introduction

The effectiveness of coronary stents in reducing angioplasty restenosis rates in de novo and restenotic lesions[1–3] and their use without systemic anticoagulation[4–6] prompted widespread acceptance of this technology. Despite these achievements, recurrence of luminal narrowing due to in-stent restenosis (ISR) occurs in a relatively high percentage of cases, when stents are implanted in complex lesions,[7] long lesions,[8,9] and small vessels.[10,11] The number of ISR cases is growing: from 100 000 patients treated worldwide in 1997 to an estimated 150 000 cases in 2001 in the USA alone.

The management of ISR has not been simple. Recurrent restenosis despite treatment is relatively high and can occur in up to 80% of cases, depending on clinical and angiographic characteristics.[12,13] As a result, prevention and treatment of ISR has been a challenge for interventional cardiology. Intravascular ultrasound (IVUS) has played a pivotal role in defining the mechanisms of ISR and optimizing the treatment, due to its ability to image the lumen and the wall of the artery in cross-section—an intrinsic advantage with respect to coronary angiography.

This review summarizes the insights provided by IVUS regarding: adequate stent implantation; mechanisms of ISR; and the results of different modalities used in the treatment of ISR.

IVUS during stent implantation

The information offered by IVUS and the use of thienopyridines resulted in a drastic change in the way coronary stents were implanted with the adoption of high pressure and no systemic anticoagulation.[4,14] At present, stent implantation without IVUS guidance has become prevalent because the performance of IVUS evaluation increases the time and cost of the procedure. In addition, a number of potential advantages with this approach have not been uniformly confirmed in randomized trials. The need for a standard to assess the adequacy of stent deployment led to the formation of IVUS defined criteria to guide stent implantation (Table 1). Despite the need for a consensus, several different

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Table 1 IVUS defined criteria for optimal stent expansion

The MUSIC Study criteria[15]
Complete apposition of the stent over its entire length
Symmetric stent expansion defined by minLD/maxLD≥0.7
In-stent minimal lumen CSA ≥90% of the average reference lumen CSA or 100% of lumen CSA of the reference segment with the lowest lumen CSA, and lumen CSA of the proximal stent entrance ≥90% of the proximal reference lumen CSA
When the minimal in-stent lumen CSA ≥9.0 mm^2 we aim to achieve
In-stent minimal lumen CSA ≥80% of the average reference lumen CSA or ≥90% of the reference segment with the lowest lumen CSA, and lumen CSA of the proximal stent entrance ≥90% of proximal reference lumen
The RESIST Study criteria[16]
In-stent minimal lumen CSA ≥80% of the average reference lumen CSA
Criterion according to Vessel CSA[4]
Minimal in-stent lumen CSA ≥60% of the average reference vessel CSA

IVUS, intravascular ultrasound; CSA, cross-sectional area; minLd, minimal lumen diameter; maxLd, maximum lumen diameter.

criteria have been proposed and are employed in different clinical studies.[15–17] The criteria used in the MUSIC (Multicenter Ultrasound Stenting in Coronaries) Study[15] have been the most widely applied (Table 1). The main difference in the criteria proposed by Colombo et al.[4] is that the latter are based on measurements of the vessel cross-sectional area (CSA), instead of the lumen CSA.

A number of clinical trials assessed the value of IVUS-guided stenting compared with angiography-guided stenting.[16–20] In the RESIST (REStenosis after Ivus guided Stenting) Study[16] 155 patients were randomized into two groups after successful stent implantation: a group without further treatment and a group with additional balloon dilatation until achievement of in-stent minimal lumen CSA ≥80% of the average reference lumen CSA. At 6 months, there was no significant difference in the restenosis rate (28.8% in the angiography-guided vs 22.5% in the IVUS-guided group, $P=0.25$), but the power of the study to establish the significance of the observed difference was only 40%. In the OPTICUS (OPTimization with ICUS to reduce stent restenosis) Study (550 patients)[17] there was also no significant difference between the groups with ultrasound-guided (using the MUSIC study criteria) or angiography-guided stent implantation, with respect to restenosis rate at 6 months (24.5 vs 22.8% respectively, $P=0.68$). In this study, the mean final lumen obtained in the angiography-guided group (2.91±0.41 mm) was larger than the original expectations, while the average lumen diameter obtained in the IVUS-guided group (3.02±0.49 mm) was less than expected. The CRUISE (Can Routine Ultrasound Influence Stent Expansion) Study (497 patients)[19] was the first study to demonstrate that ultrasound guidance of stent implantation may result in more effective stent expansion. IVUS guidance resulted in a larger post-procedure minimal stent area, compared with the angiography-guided group (7.8±1.7 vs 7.1±2.1 mm^2, $P=0.001$), which translated into a significant difference in target vessel revascularization rates at 9 months follow-up (8.5 vs 15.3%, $P=0.019$). Data supporting IVUS-guided stenting in long lesions (>20 mm) have been reported by Oemrawsingh et al.[20] There was a significant difference in target lesion revascularization (TLR, 6 vs 16%, $P=0.045$) and major adverse cardiac events (MACE, 12 vs 23%, $P=0.045$) between 73 lesions treated with IVUS-guided vs 77 lesions treated with angiography-guided stenting. Finally, in the AVID (Angiography Vs Intravascular ultrasound Directed coronary stent placement) Study[18] 800 patients were evaluated by IVUS after elective stent implantation and randomized to a group blinded to IVUS interrogation ($n=406$) and a group receiving further treatment if necessary based on the IVUS results (IVUS-guided group, $n=394$). IVUS guidance resulted in lower TLR rates for lesions with angiographic stenosis >70% in vessels with diameter <3.25 mm, as well as for stents implanted in saphenous vein grafts. The difference in TLR rates did not reach statistical significance in the entire study population (8.1 vs 12%, $P=0.08$).

It should be noted that it is not easy to achieve the IVUS criteria for stent expansion and the rates of criteria fulfillment are relatively low even in the clinical trials mentioned. Criteria achievement rates were 80% for the IVUS-guided stenting group in the RESIST and 70.7% for the IVUS-guided group in the OPTICUS Study.[16,17] Moussa et al.[21] evaluated five different criteria to define adequate stent deployment in 496 lesions treated with IVUS-guided stenting. Depending on the criteria, a successful result was achieved in only 33–82%. According to this analysis, an intra-stent minimal post-procedure lumen CSA >55% of the average reference vessel CSA measured at the media/plaque boundary, was the best criterion that combined frequency of

achievement (69% in the study) and decreased probability of restenosis (17%). Failure to achieve the criteria is worse in lesions situated in small vessels. In a retrospective study in 1580 lesions, Briguori et al. report lower fulfillment of the MUSIC criteria or the criteria proposed by Colombo et al.[4] in vessels with angiographic mean reference <3.0 mm (59.5 and 37.7%, respectively, compared to 65.6 and 51.2% in vessels >3.0 mm).[22] The achievement of either of the two criteria was associated with a lower occurrence of restenosis in small vessels. Of interest, there is often a discrepancy between angiography and IVUS in the determination of vessel size in small vessels. Some small vessels by angiography are sometimes observed to be large vessels by IVUS. This is because the definition of arterial size by angiography refers to lumen diameter at the reference site, whereas vessel size by IVUS is defined at the media/plaque boundary. Arteries with large diffuse plaque burden can be misinterpreted as small vessels by angiography. Interventions in these arteries often result in unsatisfactory outcomes because they are under-dilated. IVUS can prove essential in determining the true vessel size, leading to the use of a larger balloon and improving the results.[22] In a prospective study of 57 lesions treated with stents, published by Bermejo et al., only 57% of the lesions achieved a lumen corresponding to the size of the balloon used. Balloon under-expansion (33%) and elastic recoil (20%) were the two most important mechanisms considered responsible.[23] The presence of stent under-expansion discovered during the early stent era, has also been observed with newer stent designs. Takano et al. performed IVUS interrogation post-AVE S670 (Medtronic Inc., Minneapolis, MI, USA) or Tristar (Guidant Corp., Temecula, CA, USA) stent implantation in 38 lesions (32 patients). The mean minimal stent CSA actually achieved was only 62% of the manufacturer's expected stent area, although moderately high-pressure inflations (14–16 atm) were used.[24] If the rate of criteria fulfillment is low in the cases of IVUS-guided stenting, the percentage of stent under-expansion in everyday clinical practice without IVUS guidance is probably even higher. Obtaining the maximal achievable lumen is clinically important, since smaller post-procedure lumen dimensions are a consistent predictor of higher restenosis rates.[25–27]

Mechanisms of in-stent restenosis: IVUS observations

Two dimensional and volumetric IVUS measurements provided insights into the mechanisms of ISR and the behavior of the different parts of the stented segment. Most of the observations were carried out on Palmaz-Schatz stents (Cordis, Johnson & Johnson, Warren, NJ, USA),[28–34] although there are studies evaluating the performance of other stent designs,[35–40] as well as radioactive stents.[41–43] In a landmark study, Hoffmann et al.[28] reported the results of IVUS observations on 142 Palmaz-Schatz stents, implanted in 115 lesions. Stent restenosis was attributable to intimal hyperplasia (IH), while stent recoil was trivial. The minimum lumen CSA was located at the central articulation, due to tissue prolapse and a tendency for greater tissue accumulation. Moving away from the stent edges, there was a gradual shift from IH to negative arterial wall remodeling, in their relative contribution to lumen loss. Another report from the same center focused on the occurrence of edge restenosis. The authors studied 301 stent margins, 26% of them had restenosis. IH accounted for almost all of the late lumen loss and was significantly larger for restenotic stent edges. Stent recoil was minimal and not significantly different between restenotic and non-restenotic stent margins. The strongest predictors of edge restenosis were: (1) the post-procedure narrowing of the contiguous reference segment and (2) the degree of IH inside the stent at follow-up.[30]

The relation of IH to the stent size was assessed with the use of serial IVUS measurements for 221 Palmaz-Schatz stents (177 lesions) post-procedure and at 6-month follow-up.[31] Mean IH thickness was averaged over the length of the stent; there was no correlation between IH thickness and stent size. The independence of IH from the stent size provides an explanation for the higher restenosis rates after small vessel stenting: the same amount of IH will cause greater luminal narrowing in a small vessel. The extent and distribution of IH in asymptomatic patients was studied by Weissman et al.[32] Comparing post-procedure and follow-up IVUS in 140 patients in the course of the HIPS (Heparin Infusion Prior to Stenting) Trial, they confirmed that IH is the main mechanism of in-stent restenosis. Noteworthy in this study is that IH appeared to be a generalized phenomenon for restenotic as well as non-restenotic lesions; a Gaussian distribution of IH volume was evident, with a mean value equal to 29% of total stent volume. The authors regard IH as a biologic continuum, where only a minority of patients have an excessive form of the response. Symptoms are more likely to be related to the minimal residual lumen dimensions, rather than to the extent of IH. This fact means that the main goal

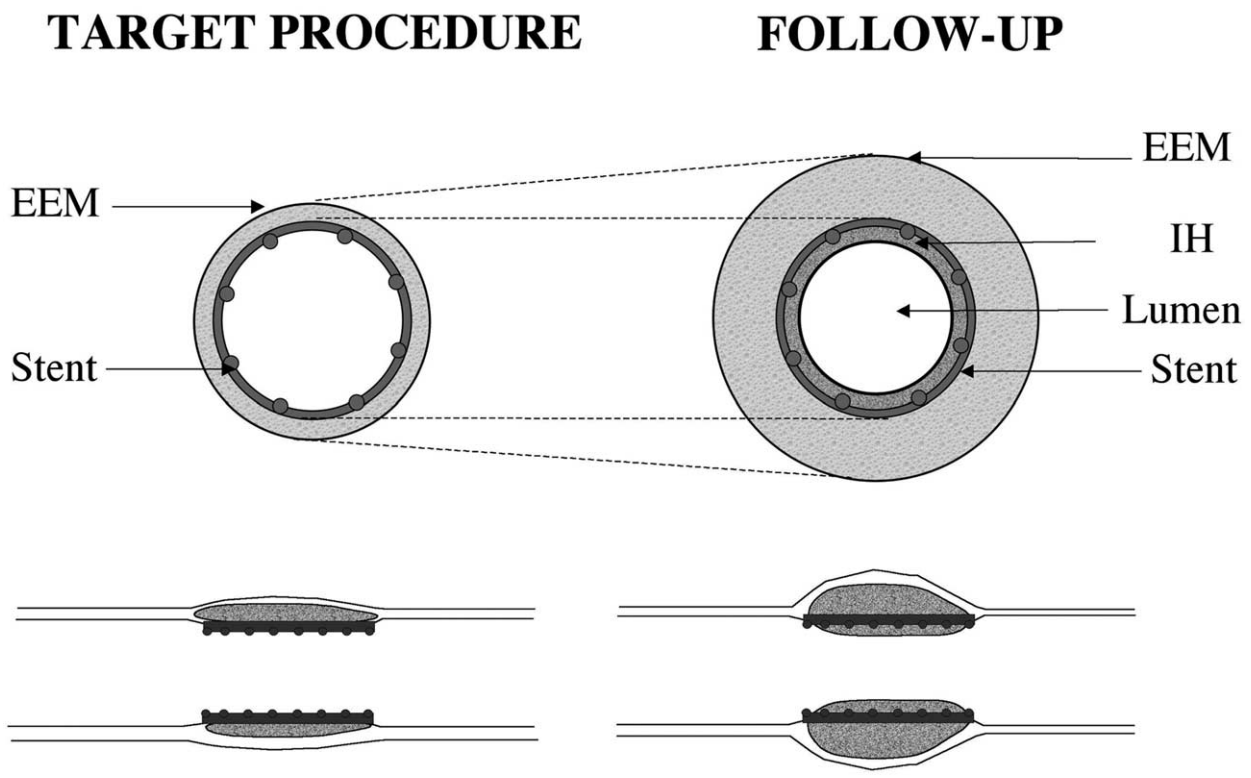

Fig. 1 Schematic representation of a lesion without positive remodeling at the time of index procedure. At follow-up after stent implantation the intimal hyperplasia is partially accommodated between the stent and the EEM with a lower amount of intimal hyperplasia compromising the lumen. EEM, external elastic membrane.

is to maximize the residual lumen rather than reduce IH.[32]

Positive arterial wall remodeling at the stent site has been reported by Hoffmann et al.[33] Serial IVUS imaging in 49 Palmaz-Schatz stents documented significant increase of vessel CSA at follow-up, which correlated strongly with mean peri-stent tissue growth. This means that following stenting there is a general increase in plaque mass; the increase around the stent causes expansion of the adventitia, while the increase inside the stent causes luminal narrowing. A further expansion of this concept to explain how remodeling can accommodate part of IH to decrease lumen loss comes from a study by Nakamura et al.[35] The authors performed serial volumetric IVUS analysis in 55 lesions treated with the ACS MultiLink stent (Guidant Corp., Santa Clara, CA, USA) and found that in segments with a lower degree of remodeling at follow-up, IH is greater and is accompanied by more significant late lumen loss. This observation could explain why artery segments with more positive remodeling at baseline develop greater amounts of IH and therefore restenosis following stenting.[44] These segments often have a larger baseline plaque mass that diminishes their ability to further compensate by expansion of the adventitia and therefore tissue grows preferentially inside the stent (Figs. 1 and 2).

The amount of plaque present at the lesion site can also influence the degree of IH following stenting.[45] Prati et al. performed volumetric IVUS measurements in 50 stents at follow-up and reported a significant positive correlation between percent residual plaque area outside the stent and percent IH area inside the stent ($r=0.50$, $P<0.01$). Shiran et al.[34] had similar findings performing serial IVUS interrogation reporting that maximal IH area was at or adjacent to the location of maximal pre-intervention plaque in 17 of 22 of the patients (77%) studied.

These observations along with the fact that the major component of restenosis following atherectomy is negative remodeling or vessel contraction[46] continue to be the basis for the possible beneficial role in combining atherectomy with stent implantation.[47–49]

Other stent types, like the self-expanding stents, have also been studied with the use of IVUS. In the SCORES (Stent COmparative RESstenosis) Study,

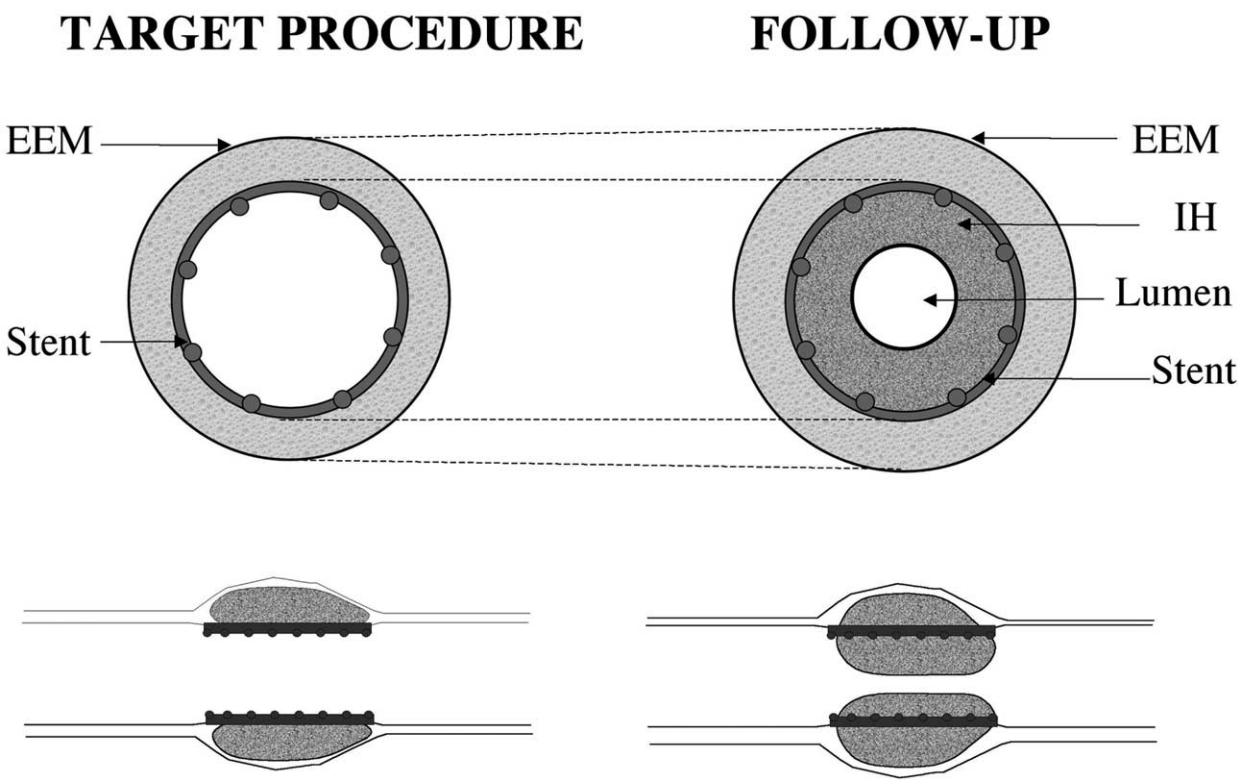

Fig. 2 Schematic representation of a lesion with positive remodeling at the time of stent implantation. At follow-up intimal hyperplasia cannot be accommodated between the stent and the EEM, which results in lumen compromise. EEM, external elastic membrane.

1096 patients were randomly assigned to receive either balloon-expandable or self-expanding stents. The incidence of MACE and restenosis was similar. In 62 patients who underwent IVUS examination, there was a trend toward a lower incidence of edge tears in the self-expanding stent group (6 vs 23%, $P=0.06$). Follow-up IVUS showed that the minimum stent area of the self-expanding stent group increased by 33% at 6 months; this was accompanied by a greater degree of IH, compared with balloon-expandable stents (3.1±2.0 vs 1.7±1.7 mm^2).[36] The Wallstent self-expanding stent (Boston Scientific, Bulach, Switzerland) has been compared to the NIR slotted tube stent (Boston Scientific, Galway, Ireland) in the treatment of long (>20 mm) lesions (44 NIR vs 41 Wallstent).[38] There was no significant difference in the rate of major events between the two groups at 6-month follow-up. There was a trend towards a lower angiographic restenosis rate in the NIR group (26 vs 46%, respectively; $P=0.1$) but the TLR rate was similar (7.9 vs 7.7%, respectively; $P=0.8$). IVUS assessment of plaque/stent ratios suggested a greater plaque burden in the Wallstent compared with the NIR stent, but again the difference was not statistically significant (0.4±1.2 vs 0.3±0.1, $P=0.1$).[38]

Two recently published reports suggest that IH is different for diverse stent designs.[39,40] Hoffman et al. performed IVUS at 6-month follow-up in 131 native coronary lesions treated with the Multilink, the InFlow (InFlow Dynamics AG, Munich, Germany), and the Palmaz-Schatz stents and detected significant difference in mean IH thickness (0.16±0.08, 0.39±0.14, and 0.26±0.19 mm, respectively, $P=0.001$).[39] Stent type was the only independent predictor of IH thickness by multivariate analysis ($P<0.001$). The authors concluded that the corrugated ring design of the Multilink stent results in less tissue proliferation at 6-month follow-up compared with the tubular slotted design of Palmaz-Schatz and InFlow stents. Yoshitomi et al.[40] randomly assigned 107 lesions to deployment of a Multilink stent or a GFX stent (Applied Vascular Engineering, Santa Rosa, CA, USA) with IVUS guidance. IVUS examination after 4 months showed larger maximal in-stent IH in the GFX group (2.9±1.7 vs 1.8±1.2 mm^2, $P<0.01$) and smaller minimal lumen diameter (2.08±0.79 vs 2.46±0.59 mm, $P<0.05$). The restenosis rate was higher in the GFX

Table 2 IVUS analysis in studies with mechanical devices in the treatment of ISR

Authors	Devices used	Number of lesions	Main findings		
				Pre-PTCA	Post-PTCA
Mehran et al.[50]	PTCA	64	MLA, mm^2	2.3±1.3	6.1±2.2*
			MSA, mm^2	7.2±2.4	8.7±2.6*
			IH area, mm^2	4.9±2.2	2.7±2.0*
				Pre-CBA	Post-CBA
Ahmed et al.[53]	CBA	10	LA, mm^2	2.8±0.9	5.8±1.6*
			SA, mm^2	7.8±3.0	8.1±2.9
			IH area, mm^2	4.9±2.4	2.3±1.4*
				ELCA	ROTA
Mehran et al.[56]	ELCA+PTCA vs ROTA+PTCA	16 vs 14	Post-procedure change in:		
			MLA, mm^2	3.72±1.78	3.64±1.58
			MSA, mm^2	0.54±1.39	0.47±0.16
			IH area, mm^2	−2.92±1.71	−3.38±1.08
				Restenting	No restenting
Mintz et al.[60]	Restenting vs no restenting	31 vs 67	Follow-up change in:	(placebo)	(placebo)
			IH area, mm^2	2.4±1.4	1.5±1.8
			MLA, mm^2	−2.7±1.2	−1.6±2.0†

*$P<0.0001$; †$P=0.058$; for other comparisons P=n.s.
IVUS, intravascular ultrasound; ISR, in-stent restenosis; PTCA, percutaneous transluminal coronary angioplasty; CBA, cutting balloon angioplasty; ELCA, excimer laser coronary angioplasty; ROTA, rotablator atherectomy; MLA, minimal lumen cross-sectional area; MSA, minimal stent cross-sectional area; IH area, mean intimal hyperplasia cross-sectional area; LA, mean lumen cross-sectional area; SA, mean stent cross-sectional area.

group (GFX 26% vs Multilink 4%, $P=0.003$). In a multiple stepwise logistic regression analysis, the only predictor of angiographic restenosis was stent type ($P<0.01$).

IVUS interrogation has also been useful in understanding the mechanism of edge restenosis following implantation of radioactive stents (the 'candy wrapper' effect).[41–43] Albiero et al.[41] were the first to report the unusual pattern of edge restenosis after implantation of ^{32}P radioactive stents. Using IVUS post-procedure and at follow-up, 122 stents were studied in the course of the Milan Dose–Response Study. Late lumen loss was primarily a result of IH in the first 2–3 mm from the stent edges, but negative arterial wall remodeling contributed to luminal narrowing in the contiguous 4–10 mm. The phenomenon of edge restenosis was also observed when a less aggressive technique of balloon dilatation and stents of higher initial radioactivity were employed.[42] In this case, negative arterial remodeling was the main mechanism of late lumen loss in the 3 mm from the stent margins. Kay et al. evaluated the implantation of 'cold-end' radioactive stents with 3-D IVUS. There was increased IH at the in-stent non-radioactive segments. The authors also detected the presence of echolucent space representing areas of non-apposition of the stent struts (initially called 'black holes') in six out of the eight cases of restenosis.[43] This was presumably due to retraction of tissue secondary to the radiation.

Treatment of in-stent restenosis: IVUS insights

There is a wide spectrum of conventional catheter-based techniques for treatment of ISR, ranging from plain balloon angioplasty to various atherectomy devices and repeat stenting. Some of the published reports include IVUS interrogation[50–61] (Table 2). The long-term outcome is heavily influenced by the pattern of ISR, as described by Mehran et al.[13] This classification, although angiographic, was verified by IVUS interrogation. Restenosis rates vary from 19% in focal up to 50% in proliferative (extending beyond the stent margins type of ISR) and reach 83% after treatment of intrastent total occlusion.

Balloon angioplasty

The use of balloon angioplasty (PTCA) in ISR has been evaluated by Mehran et al.[50] They studied 64 restenotic Palmaz-Schatz stents, performing IVUS measurements at five stent segments before and after PTCA (Table 2). Additional stent expansion accounted for 56% of the total mean lumen enlargement. The remainder of the enlarged lumen

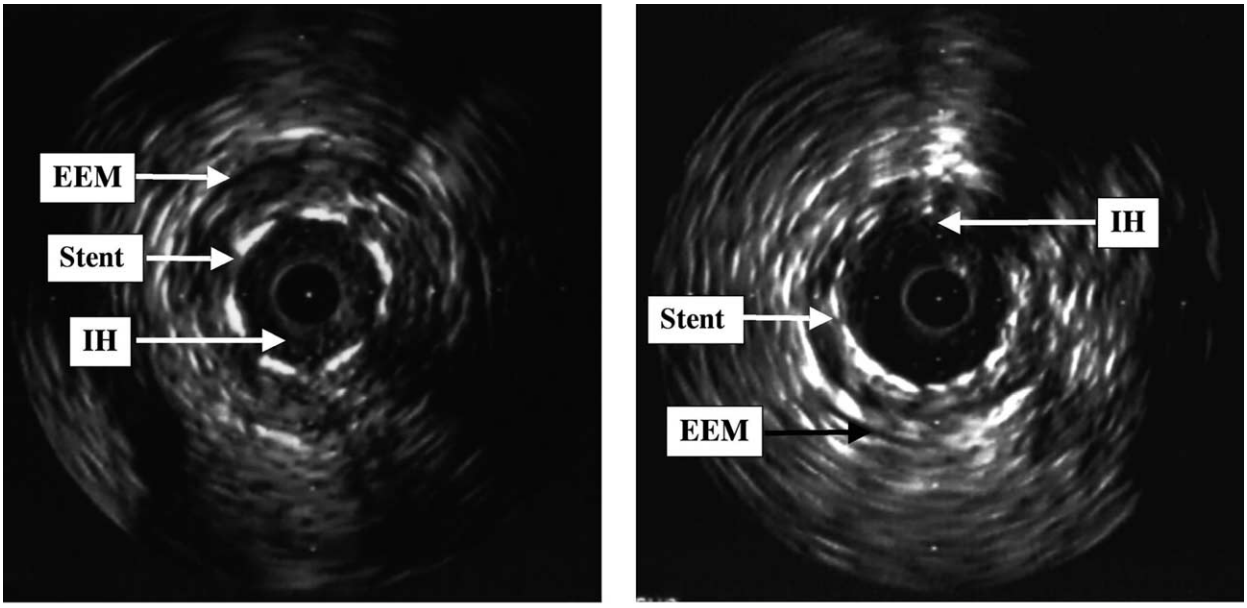

Fig. 3 (Left panel) IVUS image of a restenotic segment 6 months after stent implantation. The stent was under-expanded relative to the vessel dimensions. Also, tissue proliferation within the lumen of the stented segment causes significant lumen narrowing. (Right panel) After treatment with a 3.0 mm cutting balloon there is stent re-expansion with a decrease of neo-intimal tissue, which has been extruded behind the stent. CSA, cross-sectional area; EEM, external elastic membrane; IH, intimal hyperplasia.

(44%) was due to a decrease in neo-intimal tissue, which was attributed to plaque redistribution. Sakamoto et al.[51] randomized 37 restenotic Palmaz-Schatz stents into two groups: an angiography-guided PTCA group and an IVUS-guided group, where the balloon diameter was equal to 95% of the IVUS media to media diameter distal to the stent. Balloon to artery lumen ratio was 1.16 and 1.33, respectively. There was a remarkably low restenosis rate in the IVUS-guided PTCA arm (17%), which resulted in a statistically significant difference in restenosis rates (53% in the angiography-guided group, $P<0.05$).

Cutting balloon angioplasty

There are no clear-cut IVUS data concerning the mechanisms of acute lumen gain when cutting balloon angioplasty (CBA) is used for ISR (Fig. 3). Most of the data come from small observational studies.[52–54,62] Kinoshita et al. compared IVUS findings post-PTCA ($n=12$) and post-CBA ($n=19$) and reported that the vessel and stent volumes increased more in the PTCA group (vessel volume difference: 10.0±10.8 vs 1.9±7.8%, $P=0.02$ and stent volume difference: 22.3±14.0 vs 9.9±9.8%, $P=0.007$).[52] It is not clear whether plaque compression or extrusion of plaque contributes to the lumen gain when CBA is used for ISR. RESCUT (REStenosis CUTting balloon evaluation) is a current European multi-center clinical trial comparing CBA with PTCA in ISR. There is an ancillary IVUS substudy that should help define the difference in the mechanisms of the two techniques. IVUS interrogation performed 15–30 min post-procedure will identify early tissue re-intrusion or stent/vessel recoil in lesions treated with CBA, as compared to those treated with PTCA and the role of further stent expansion.

Debulking techniques

Different debulking techniques, like excimer laser coronary angioplasty (ELCA) and rotablator atherectomy (ROTA) have been used to treat ISR in conjunction with PTCA; their mechanisms and relative effectiveness have been assessed by IVUS.[55–58] Mehran et al. performed volumetric IVUS analysis in 54 lesions treated with ELCA and PTCA and reported that the ablative technique contributed 29% to the achieved acute lumen gain. However, the mechanical effect of passing the laser catheter without

turning it on was not assessed. The residual 71% was due to adjunct PTCA: 40% resulted from additional stent expansion and 31% from plaque extrusion.[55] In a comparison of ROTA+PTCA (n=161 lesions) with ELCA+PTCA (n=158 lesions) for ISR treatment[56] Mehran et al. did not find a significant difference in post-intervention minimal lumen diameter (MLD) or lumen CSA. Angiographic success and major in-hospital complications were also similar with the two techniques. Using volumetric IVUS analysis in a subset of lesions (ROTA n=14, ELCA n=16),[56] a higher ablation efficiency of ROTA was demonstrated: 43% IH volume reduction compared with 19% IH reduction in the lesions treated with ELCA. Adjunct PTCA was responsible for more than half of the overall lumen gain in both groups (54% in ROTA+PTCA and 73% in ELCA+PTCA) and equalized the final lumen dimensions (Table 2). In-stent post-procedure residual IH (29% for ROTA and 27% for ELCA) and residual stenosis (18–22%) underlined the limitations of both approaches. Radke et al. have reported similar observations after IVUS interrogation of 49 lesions treated with ROTA+PTCA. Plaque removal during ROTA resulted in 37% of acute lumen gain; further stent expansion and plaque extrusion during adjunctive PTCA contributed 49 and 14% of acute lumen gain, respectively.[57] Another evaluation of the relative contribution of ROTA and PTCA after successful treatment of 100 ISR lesions was provided by Sharma et al.[58] The authors reported that 77% of the acute lumen gain was due to rotational ablation of the restenotic tissue and only 23% occurred after adjunct balloon dilatation. The discrepancy in relation to the previous studies may be due to their more aggressive use of ROTA.

It is of clinical importance to note that the long-term outcome depends on the lumen dimensions achieved post-procedure, regardless of the type of procedure. This is emphasized in a prospective study with 1-year clinical follow-up of 70 patients after PTCA or ROTA+PTCA for ISR. The only independent predictor of event-free survival was the lumen size achieved, regardless of the means used to achieve it.[63] A 4.7 mm^2 lumen CSA cut-off point determined follow-up events in the study. An interesting observation was reported by Shiran et al.,[59] who performed IVUS in 37 ISR lesions 42±8 min post-procedure (ELCA+PTCA, ROTA+PTCA or only PTCA). By this time following the procedure a significant 20% reduction of lumen CSA was observed due to tissue prolapse back into the stent. In 27% of the lesions studied, there was more than 2.0 mm^2 reduction in lumen area. This phenomenon was observed regardless of treatment modality. Plaque prolapse was greater in longer lesions, in those with a large in-stent plaque burden and was not detected by coronary angiography (Fig. 4).

Re-stenting

IVUS data at follow-up are reported by Mintz et al. in 31 patients with diffuse ISR treated with additional stent implantation compared with 67 patients without additional stenting.[60] All patients were enrolled in either the irradiation or control group of the WRIST (Washington Radiation for In-STent restenosis) Study. Minimal lumen CSA tended to be lower (P=0.058) in patients with 'stent on stent' compared to all other treatments in the non-radiated group (Table 2). In patients treated with ^{192}Ir there was no difference detected. The authors concluded that additional stent implantation retriggers IH, an effect neutralized by γ-radiation.

Brachytherapy

IVUS has been utilized to define the mechanisms of intracoronary brachytherapy, to elucidate its potential complications[64] and as a dosimetry tool.[65,66] Radiation dose based on IVUS measurements may be used to improve safety and efficacy of brachytherapy. The recommendations for utilizing γ-radiation stress the importance of avoiding more than 30 Gy at the closest target (intima) and giving at least 8 Gy at the farthest target (adventitia).[66] The utility of this approach used in the SCRIPPS and GAMMA-1 trials has been questioned because similar clinical results were obtained in studies which did not use IVUS as a dosimetry tool.[67]

IVUS analysis results are reported in many of the published studies.[68–76] Mintz et al. have reported post-procedure and 8-month follow-up IVUS analysis for 70 patients enrolled in the GAMMA-1 trial[68] (Table 3). When averaged over the entire stent length, the increase in IH was 0.8 mm^2 for the irradiated group compared with 1.6 mm^2 for the control group (P=0.0065). ^{192}Ir therapy inhibited IH within the stent without exerting a significant effect on the stent edges. Similar IVUS results were obtained in the WRIST Study[69] comparing patients randomized to receive either intracoronary γ-radiation with ^{192}Ir or placebo after successful treatment of ISR (Table 3). The minimal lumen CSA change at follow-up was lower in the ^{192}Ir group (0.4±1.9 vs 1.9±1.6 mm^2, P<0.0001) due to smaller increase in IH volume (3.1±38.4 vs 55.0±60.1 mm^3, P<0.0001). It is noteworthy to mention that more

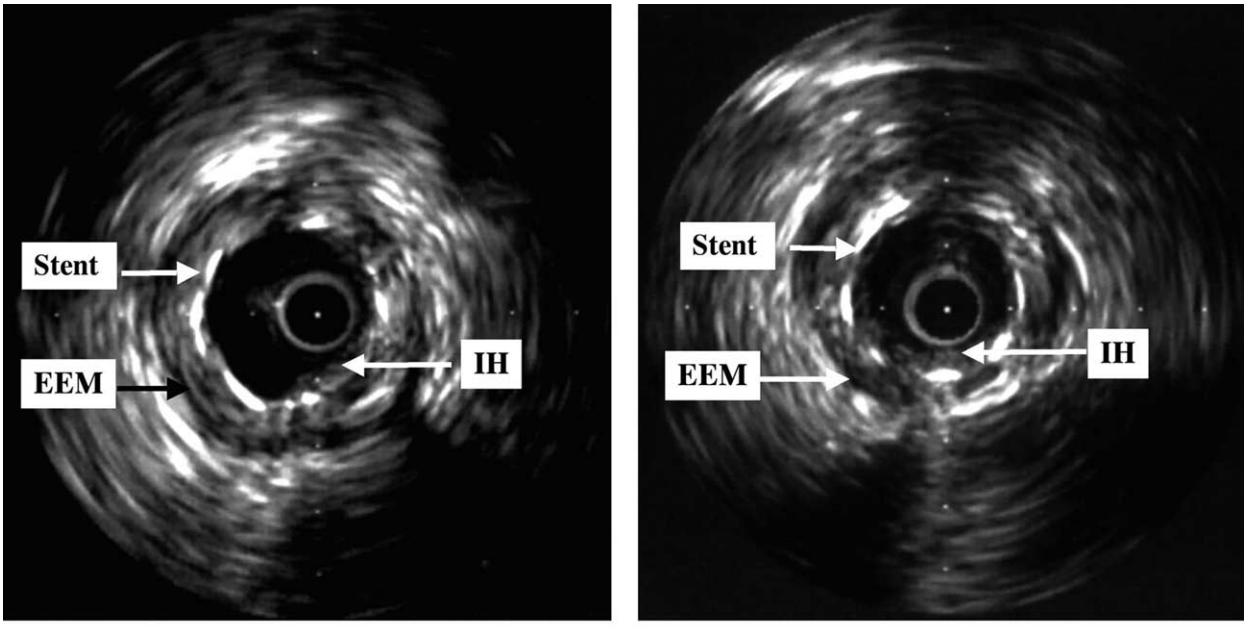

Fig. 4 (Left panel) IVUS image of a restenotic segment after treatment with 3.5 mm balloon angioplasty. There is a small amount of residual neo-intimal tissue. (Right panel) Increased amount of neo-intimal tissue inside the stent lumen in the IVUS image 15 min post-procedure. CSA, cross-sectional area; EEM, external elastic membrane; IH, intimal hyperplasia.

Table 3 IVUS analysis in studies of intracoronary radiation for treating ISR

Study	Isotope	Patient number		Main findings		
				Radiation		Placebo
GAMMA-1[68]	^{192}Ir	37 vs 33	ΔIH volume:	28±37	vs	50±40 mm^{3†}
			ΔMLA:	1.0±1.3	vs	2.2±1.8 mm^{2†}
WRIST[69]	^{192}Ir	54 vs 57	ΔIH volume:	3±38	vs	55±60 mm^{3*}
			ΔMLA:	0.4±1.9	vs	1.9±1.6 mm^{2*}
Long WRIST[70]	^{192}Ir	28 vs 30	ΔIH area:	0.64±1.6	vs	2.3±1.5 mm^{2*}
			ΔMLA:	0.61±1.0	vs	2.3±1.3 mm^{2*}
START[72]	^{90}Sr/Y	17 vs 12	ΔIH area:	−1.3±18.4	vs	25.4±25.4 mm^{2¶}
BETA-WRIST[71]	^{90}Y	25 (no placebo)	ΔIH volume:	16±30 mm^3		
			ΔMLA:	1.0±1.4 mm^2		

*P<0.0001; $^{\P}P$<0.01; $^{\dagger}P$<0.05.
IVUS, intravascular ultrasound; ISR, in-stent restenosis; ^{192}Ir, Iridium-192; ^{90}Y, Yttrium-90; ^{90}Sr, Strodium-90; ΔIH volume=the difference of intimal hyperplasia volume at follow-up−intimal hyperplasia volume at target procedure; ΔMLA=the difference of minimal lumen cross-sectional area at target procedure−minimal lumen cross-sectional area at follow-up; ΔIH area=the difference of intimal hyperplasia cross-sectional area at follow-up−intimal hyperplasia cross-sectional area at target procedure.

than half of the irradiated lesions demonstrated a reduction in IH between the target procedure and follow-up ('melting' of hyperplasia); a finding without a definite explanation that suggests persistent apoptosis and remodeling may occur post-radiation. Ahmed et al.[74] focused on stent edge restenosis by performing serial IVUS analysis in eight patients with recurrence compared with 21 without recurrence, all treated with ^{192}Ir in the WRIST Study. Lumen loss was attributed to increased IH, combined with the absence of radiation induced positive arterial wall remodeling in the cases with geographic miss.

Beta radiation therapy has also been evaluated in the treatment of ISR. Fifty patients with ISR were treated with a β-emitter (^{90}Y) in the course of the

BETA WRIST registry study[71] (Table 3). Minimal lumen area decreased (1.0±1.4 mm^2) and IH volume increased (16±30 mm^3) significantly less than the respective values seen in the control group of the WRIST Trial. In the START (STents and Radiation Therapy) Trial treatment with a $^{90}Sr/^{90}Y$ source was compared with placebo. Takagi et al.[72] reported that the mean follow-up minimal lumen CSA was significantly higher in the irradiated group (4.2±2.0 vs 2.6±1.4 mm^2, $P<0.05$) (see also Table 3). The comparative efficacy of β-radiation vs γ-radiation therapy has been evaluated with 3-D IVUS in a report by Bhargava et al.,[73] assessing post-procedure and follow-up IVUS results in 25 patients from the BETA-WRIST Trial and 75 patients from the WRIST Trial. The amount of increase of IH and decrease of lumen volume was similar for beta and gamma radiation: the change in IH volume between post-procedure and 6-month follow-up was 16± 30 mm^3 for β-radiation compared with 9±38 mm^3 for γ-radiation therapy.

Finally, a report on 66 patients enrolled in the WRIST and Long WRIST Trials correlated the length of ISR with the source-to-target distance and an index of source eccentricity within the artery.[75] The longer the lesion, the greater the variability in cross-sectional geometry and the actual dose delivered at the adventitia. The authors suggest that source-to-target distance heterogeneity may account for the reduced effectiveness of brachytherapy in longer ISR lesions. A higher dose of irradiation (18 Gy at 2.0 mm from the source) as in the high dose Long WRIST (HD Long WRIST) Trial seems to surmount the problem. Ahmed et al. reported on IVUS findings in 30 patients from Long WRIST compared with 25 patients from the HD Long WRIST Trial. At follow-up, the minimal lumen CSA was larger in the high-dose group (4.0±1.4 vs 2.9±1.0 mm^2, $P<0.0009$).[76]

Drug-eluting stents

One of the most promising approaches to prevent IH in a safe and durable way relies on the deployment of drug-eluting stents. The first IVUS studies evaluating the implantation of drug-eluting stents in de-novo coronary artery lesions contribute to the general optimism that these new devices may be the vehicle that overcomes the development of IH.[77–79] Sousa et al.[77] used 3-D IVUS to study 30 patients treated with two different formulations of sirolimus-eluting stents (slow release, $n=15$, and fast release, $n=15$). At 4-month follow-up there was minimal IH in either group (16.8±6 mm^3 in the slow release group and 13.3±4 mm^3 in the fast release group, P=n.s.). No in-stent or edge restenosis was observed. No major clinical event (stent thrombosis, repeat revascularization, myocardial infarction, or death) had occurred by 8 months of clinical follow-up. The same group has reported angiographic and IVUS measurements at 1 year follow-up. In-stent MLD and percent diameter stenosis remained essentially unchanged in both groups; IH was virtually absent.[78] IVUS analysis post-intervention and at 8.3 months follow-up was performed in 15 native coronary lesions treated with the QuaDS-QP2 stent.[79] Mean IH area within the stent at follow-up was 1.2±1.3 mm^2, and mean cross-sectional narrowing (neo-intimal area/stent area) was 13.6±14.9%. At the vessel segments immediately adjacent to the stent, a significant increase in plaque area (1.9±2.6 mm^2, $P=0.001$) was observed, but there was no clinically significant in-stent or edge restenosis during the follow-up period. Late non-apposition of the stent struts has been observed by IVUS following the implantation of drug-eluting stents. At the 6-month follow-up study, some lesions show small areas of free space between the stent struts and the inner vessel wall. This finding has been described to be present in as much as 20% of lesions treated with a sirolimus-eluting stent (personal communication, M.C. Morice). An IVUS follow-up scheduled at 18 months will help clarify the long-term evolution of this finding which to date has not caused any unfavorable clinical event.

There are also pilot studies evaluating the implantation of drug-eluting stents in ISR lesions with initial encouraging results. Sousa et al.[80] reported the first human experience of sirolimus-eluting stents for the treatment of ISR using IVUS interrogation at the index procedure and at follow-up. Thirty patients with ISR were treated (implantation of 41 stents) and stent thrombosis was not detected up to 30 days. Angiographic follow-up at 4 months has been completed in 17 patients without any restenosis; IH was 6.3±5.6 mm^3 in that subset of patients.

Conclusions

IVUS observations have contributed significantly to our understanding of coronary pathology and how to optimize stent implantation, so that this procedure can be performed safely with improved results. IVUS interrogation has identified IH as the main cause of ISR. IVUS has outlined the limits of the different modalities used to counteract ISR. When using mechanical methods to treat ISR, lumen dimensions post-repeat procedure determines the

recurrence rate, regardless of the mode of treatment. However, the application of antiproliferative approaches such as intracoronary radiation and drug-eluting stents has resulted in a new era of optimism for the treatment of restenosis and ISR. Until we have long-term follow-up of the effects and safety of radiation and drug-eluting stents, accomplishment of the highest lumen dimensions possible at the time of stenting and at the time of treatment of ISR will be the best route available to lower the clinical consequences of ISR.

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