The Biology of In-Stent Restenosis and the Rationale for Debulking

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ABSTRACT: Over the past several decades, new devices have been developed for endovascular therapy of arterial occlusive disease in the superficial femoral and infrapopliteal arteries. These new technologies and techniques have brought about an increase in endovascular treatment with stenting. With the increase in stenting has come an increase in the incidence of in-stent restenosis. Currently, there is a trend toward use of drug-coated balloon angioplasty instead of stents, and this is expected to lead to a significant reduction in the number of stents that will be implanted in the superficial femoral artery. However, bail-out stenting after drug-coated balloon angioplasty can be as high as 40% in long lesions. Therefore, ISR will remain a problem with a significant effect on mid- and long-term outcomes of SFA stenting. This paper will provide a description of the biology of in-stent restenosis as well as an overview of the literature on the treatment of in-stent restenosis using various available techniques and the role of debulking.

Key words: endovascular therapy, superficial femoral artery, in-stent restenosis, occlusion, atherosclerosis

New techniques and technologies have been developed in the past several decades for the endovascular treatment of arterial occlusive disease affecting the superficial femoral artery (SFA) and infrapopliteal arteries. Dedicated stents have been extensively used to address the problem of elastic recoil, flow-limiting dissection, and residual stenosis after balloon angioplasty. Their development has allowed the treatment of very complex and extensive lesions with a low complication rate. As a result of the favorable outcomes that can be achieved (as compared to plain balloon angioplasty), endovascular treatment with stenting has become the treatment modality of choice, with a total number of more than 80,000 stents implanted in the United States in 2014 (number based on the volume of Medicare patients that constitutes 70% of all-payer volume; source The Advisory Board Company, personal communication). Restenosis rates in the various randomized
controlled trials (with an average lesion length <10 cm) was in the range of 20% at 1 year. In daily practice treated lesion length is typically longer, and therefore higher restenosis rates can be expected. Thus the problem of in-stent restenosis (ISR) is occurring more frequently. Currently there is a tendency to abandon the primary use of stents (and use drug-coated balloon angioplasty instead), and this is expected to lead to a significant reduction in the number of stents that will be implanted in the SFA, but stenting of the SFA will not become obsolete (bail-out stenting after drug-coated balloon angioplasty can be as high as 40% in long lesions). Therefore, ISR will remain a problem affecting mid- and long-term outcome of SFA stenting significantly.3

This paper will provide a description of the biology of (in-stent) restenosis. Furthermore it will give an overview of the literature with the treatment of ISR using various available techniques and the role of debulking.

THE BIOLOGY OF RESTENOSIS

All endovascular procedures (balloon angioplasty with or without stenting) produce a more or less controlled injury to the arterial wall, with intimal plaque disruption typically accompanied by medial injury. Deep injury of the vessel wall caused by stent struts (that damage the internal elastic lamina), is one of the causes of restenosis.4

The local arterial response to stenting as demonstrated by experimental animal and human autopsy studies follows a response-to-injury sequence of events that is comparable to that of wound healing.5-7 The SFA, like the coronary arteries, is a so-called muscular or distributing artery. Muscular arteries contain more smooth muscle cells and fewer elastic muscle cells than elastic arteries. Elastic arteries typically contain high amounts of collagen and elastin fiber in the media, and exhibit a lower incidence of ISR.8 The ISR mechanism in coronary and peripheral muscular arteries supposedly is similar9: stents cause platelet and fibrin deposition around struts in human coronary arteries. An initial acute inflammatory cell response is seen within the first 3 days. This acute inflammation will subside and is followed by a granulation tissue response with neovascularization, smooth muscle cell migration and proliferation, and replacement of acute inflammatory cells by chronic inflammatory cells in a period extending from 2 to 4 weeks: proliferating smooth muscle cells are seen in the early neointima and are associated with organizing thrombus and a thin extracellular matrix. After 30 days, the presence of fibrin and chronic inflammation may persist.

The neointima is enriched further by smooth muscle cells and extracellular matrix. The formation of intimal hyperplasia (restenosis) consists of 3 distinct processes: cell replication, cell migration, and accumulation of extracellular matrix in the arterial wall.10 The extracellular matrix molecules are synthesized by neointimal smooth muscle cells. The extracellular matrix is composed of a variety of molecules, including collagen (type I and III), elastin, glycoproteins, and proteoglycans (versican, biglycan, and decorin). Proteoglycans and hyaluronan participate in the regulation of vascular permeability, lipid metabolism, and thrombosis. In a muscular artery, type III collagen is the most abundant matrix protein.
Experimental arterial injury studies have demonstrated that remodelling of the neointima occurs with replacement of type III collagen with type I collagen. The extracellular matrix accumulates mainly around stent struts and in the outer intima.10,11 Around the struts, in addition to the extracellular matrix, inflammatory cells (leukocytes, macrophages, and T-lymphocytes) can be found. The outer intima is characterized by lower cell density or lower cell replication compared to the inner intima, which suggests that matrix accumulation is more critical than the increase of cell number because of cell replication. Smooth muscle cell components are concentrated at the intimal surface, and even at 7 to 19 months after stent implantation cell replication can be demonstrated.10 This dense neointimal layer is typically the first 250 μm of the intraluminal section.

Studies with animal models that have evaluated the responses to balloon angioplasty injury of arteries with preexisting intimal lesions showed similar findings in the intima after balloon angioplasty. Intimal size increases in the late phase after balloon angioplasty, and matrix accumulation (and not intimal cell replication) accounts for most of the increase of intimal size.10 A difference exists in restenosis mechanism between balloon angioplasty and stenting. Intimal hyperplasia accounts for all late lumen loss following stenting, but for less than 40% after balloon angioplasty (the remainder being caused by so-called constrictive remodelling). Stenting causes an even greater increase in collagen accumulation, in both arterial intima and media/adventitia layers compared with balloon angioplasty. This is due to extensive tissue damage and persistent circumferential stretching, that are both well recognized stimuli for enhanced collagen synthesis.12,13

The major histological findings in ISR can be summarized as follows:

- In-stent restenotic lesions are complex and differ significantly from de novo atherosclerotic lesions.
- In-stent restenotic lesions are heterogeneous and consist primarily of collagen and smooth muscle cells, with a high water content. They have an innermost intimal layer of dense smooth muscle cell tissue and an outermost intimal layer that can be described as a cell-poor scaffold or “sponge” comprised of collagen. This outermost intimal layer is the largest volume constituent of an in-stent restenotic lesion.
- Calcium is rarely present in in-stent restenotic lesions.

**TREATMENT OF IN-STENT RESTENOSIS**

The characteristics described herein have important implications for the treatment of ISR in the femoral artery.

The luminal gain obtained with balloon angioplasty for coronary ISR involves 3 mechanisms: Tissue compression (by squeezing out the water content of the neointimal hyperplasia), extrusion of tissue out of the stent, and additional stent expansion. The latter may account for up to 56% of the total luminal gain.14 Both tissue compression and extrusion can take place during PTA of self-expanding stents as well, but additional stent expansion can not be obtained (the stent being already fully expanded).

In a volumetric analysis (using intravascular ultrasound) of patients treated with PTA for coronary
ISR, it was found that after approximately 30 minutes the intrastent tissue volume increased by 32% (immediately after PTA an intrastent tissue volume decrease of 50% was noted). In addition to the lack of further stent expansion and the quick recoil of the compressed tissue, the process of positive remodeling that occurs in the native SFA when a stenotic lesion develops is no longer possible after stent placement. Because of these factors, which are completely different from primary atherosclerotic lesions, balloon angioplasty will not be efficacious and thus the treatment of ISR requires a completely different approach. Multiple therapeutic modalities have been used to deal with the problem of SFA ISR, and an overview of the results will be presented hereafter.

CONVENTIONAL AND CUTTING BALLOON ANGIOPLASTY

In a randomized study that compared conventional balloon angioplasty with peripheral cutting-balloon angioplasty in patients with ISR, with lesion lengths up to 20 cm (mean lesion length 80 mm), it was found that restenosis rates at 6 months with conventional PTA were 73%, and with cutting balloon angioplasty they were slightly lower (65%). Likewise, the study by Tosaka et al showed that the rate of recurrence of ISR after balloon angioplasty was significant, being the highest in class III lesions (84.8%) and lower in class II and I (53.3% and 49.9%, respectively). Another study evaluating 75 cases using the Tosaka classification revealed similar results, with repeat restenosis during 2-year follow-up of 39% for class I, 67% for class II, and 72% for class III and rates of stent occlusion of 8%, 11%, and 52% for class I, II, and III respectively. Confounding these findings is the fact that in this study, balloon angioplasty was not the only treatment used (combined treatment with cutting balloon angioplasty, laser atherectomy or additional [covered] stent placement).

Because of these poor outcomes, many clinicians have abandoned balloon angioplasty to treat ISR, particularly in long or occlusive disease, and started a quest for alternative treatments, including cryoplasty, drug-eluting stents, and drug-eluting balloons, covered stents, and various types of atherectomy.

CRYOPLASTY

Cryoplasty for ISR resulted in even worse outcome data compared to balloon angioplasty, with a 100% failure rate at 12 months in one study and a primary patency rate at 6 months of 43.8% in another. Cryoplasty is no longer commercially available.

DRUG-ELUTING STENTS

The results obtained with the Zilver (Cook Medical) paclitaxel-eluting stent in the treatment of femoral ISR are better, with a primary patency rate at 1 year of 78.8% and a freedom from target lesion revascularization (TLR) rate at 1 and 2 years that was 81% and 60.8%, respectively. It has to be kept in mind that additional stenting augments the risk of stent fractures (1.2% in this study). The relatively few length options for drug-eluting stents (as compared to covered stents), and the occurrence of stent fractures (although the incidence is low) may limit utility and cost effectiveness. Whether the results of DES using the Zilver PTX for ISR are better than bare metal stenting using the latest generation stent
designs is not known (although the results of the randomized trial in primary lesions demonstrated a significant benefit of the drug-eluting Zilver stent as compared to the Zilver (noncoated) stent, the results at 1 and 2 years were not superior to newer design (bare metal) stents in other trials).²,²⁴-²⁶

**Covered Stents**

The results of the use of covered stents in SFA ISR as described in the literature are not unequivocal. The SALVAGE study yielded a disappointing primary patency at 12 months of 48%, with a low 12-month TLR rate (17.4%).²⁷ Different, and better results were seen in the RELINE study.²⁸ The 12-month primary patency rate for covered stents was 74.8%, with a freedom from TLR at 12 months of 79.9%. An explanation for these differences in outcome cannot be given.

**Drug-Coated Balloon Angioplasty**

Several studies have evaluated the use of drug-eluting balloons for the treatment of superficial femoral artery ISR. The first study (registry) that was published demonstrated a 92.1% primary patency rate at 1-year follow-up. In this study the number of Class III lesions was relatively low (20.5%), while 30.8% of the lesions was class I and 48.7% was class II.²⁹ At 1 year no influence of lesion length on outcome was seen. The results of 2-year follow-up showed a decrease in primary patency to 70.3% (11 of 37 patients experienced restenosis recurrence at 2-year follow-up) and a freedom from TLR of 78.4%. At 2 years a difference in outcome was seen in relation to lesion complexity and/or length. The treatment of complex ISR lesions (classes II and III) was associated with a higher rate of recurrent restenosis than those patients with class I lesions (33.3% and 36.3% respectively vs 12.5%; \( P=.05 \)).³⁰

The second registry, the DEBATE-ISR study, compared a group of 44 diabetic patients that was treated for femoropopliteal (FP) ISR with drug-coated balloons with a historical control group of 44 diabetic patients treated with conventional balloon angioplasty.³¹ At 1 year, restenosis was seen in 19.5% patients in the DCB group vs 71.8% in the conventional balloon angioplasty group (\( P<.001 \)). Target lesion revascularization for symptomatic recurrent restenosis was performed in 13.6% of patients in the DCB group while 31% of the patients in the PTA group underwent repeat intervention (\( P=.045 \)). At 3-year follow-up a complete catch-up was seen, without any difference between DEB and POBA.³² Especially in the treatment of more complex ISR lesions (Tosaka class III) there is an increased rate of TLR, irrespective of the technology used (DEB or conventional balloon angioplasty).

The most recent study to be published is the FAIR trial (randomized controlled trial).³³ Binary restenosis at 6 months as assessed by Duplex was 15.4% in the DCB group and 44.7% in the conventional PTA group. At 12 months, the incidence of recurrent restenosis was 29.5% and 62.5% respectively. The freedom from TLR was significantly higher in the patients that were treated with DCB (96.4% vs 81% at 6 months, 90.8% vs 52.6% at 12 months).

**Debulking and Atherectomy**

Removal of the neointimal hyperplasia and extra-
cellular matrix is an attractive option from a theoretical point of view. Both mechanical atherectomy and laser debulking have been described as potential favorable techniques. All current (mechanical) atherectomy devices rely on scraping or grinding using moving components that pose an elevated risk for stent disruption and fragmentation or device entrapment. Directional atherectomy, and other methods of mechanical atherectomy (orbital or rotational) are actually contraindicated in the treatment of ISR and this technique is therefore not recommended, and these devices, intended for use in calcified lesions, may lead to higher embolization rates in soft ISR lesions. Directional atherectomy as standalone treatment has been demonstrated to be inadequate in the treatment of ISR, with patency rates around 50%. Trentmann et al showed an even lower primary patency rate at 1 year of 25%. A retrospective single-center analysis by Shammas et al showed a freedom from TLR rate at 1 year of 68.3% for the directional atherectomy group and 51.3% for the laser-treated patients.

Three large studies have been published on ablation with excimer laser, which does not involve any moving parts, and currently is the only FDA-approved device for ISR. These include the multicenter PATENT registry, a dual-center report, and the EXCITE multicenter randomized trial. In the PATENT study, the primary patency at 6 months (64.1%) compared favorably to plain or cutting balloon angioplasty. At 12 months the overall primary patency showed a drop to 37.8%. The primary patency at 12 months as stratified by Tosaka class was 54.5% for class I, 27.6% for class II, and 24.0% for class III. These results indicate that longer and more complex lesions tend to do worse. In the dual-center nonrandomized study the procedural success was higher in the laser group (100% vs 98%), but laser atherectomy was complicated more frequently by distal embolization (9% vs 1%, \( P=.01 \)) and had a higher rate of provisional stenting (59% vs 37%, \( P=.01 \)). Patients were stratified in class I/II and class III FP ISR according to Tosaka. In the first group (class I/II) there was no significant benefit of laser atherectomy on the rate of recurrent restenosis at 2 years (69% vs 46%, \( P=.2 \)) or stent occlusion (26% vs 12%, \( P=.2 \)). Patients with class I/II lesions that were treated with laser atherectomy had significantly lower rates of TLR at 2 years (14% vs 44%, \( P=.05 \)). Worth noting is that patients with class I/II FP ISR who were treated with laser atherectomy had lengthier restenotic lesions (129±86 vs 89±86 mm, \( P=.09 \)), suggesting that laser atherectomy was preferentially used for more complex lesions even when not dealing with stent occlusion. In class III in-stent restenotic lesions, laser atherectomy was associated with significantly lower rates of recurrent restenosis at 1 year (54% vs 91%, \( P=.05 \)) and 2 years of follow-up (69% vs 100%, \( P=.05 \)). The overall rates of TLR were similar between the groups (43% vs 48%), but laser atherectomy was associated with significantly lower rates of recurrent in-stent occlusion at 2 years (33% vs 71%, \( P=.04 \)). Similar results were obtained in the multicenter, prospective, randomized, controlled EXCITE ISR trial that evaluated laser atherectomy combined with PTA and PTA as standalone treatment. Laser atherectomy combined with PTA subjects demonstrated superior
procedural success (93.5% vs 82.7%; \( P = 0.01 \)) with significantly fewer procedural complications. Laser atherectomy and PTA and PTA subject 6-month freedom from TLR was 73.5% vs 51.8% (\( P < 0.005 \)), and 30-day major adverse event rates were 5.8% vs 20.5% (\( P < 0.001 \)), respectively. Laser atherectomy and PTA was associated with a 52% reduction in TLR (hazard ratio: 0.48; 95% confidence interval: 0.31 to 0.74). Patients in the laser atherectomy with PTA group demonstrated significantly better improvement or maintenance of Rutherford category (\( P = 0.008 \)). Especially in long-length ISR, a benefit of laser atherectomy and PTA vs. PTA was seen. The PATENT and EXCITE studies demonstrated lower provisional stent rates, probably related to the use of Turbo-Tandem/Turbo-Booster catheters (Spectranetics), which provide a higher degree of debulking as compared to the Turbo-Elite catheters (Spectranetics) used by Armstrong et al. The long-term results remain suboptimal however, and therefore combination therapy of debulking and drug-coated balloons has been proposed as an emerging therapy.

**DEBULKING AND DRUG-COATED BALLOON ANGIOPLASTY**

The technique of the combined therapy of laser debulking and drug-eluting balloon angioplasty for ISR has been discussed extensively. The short-term follow-up (mean of 7.6 months) of a cohort of 10 patients treated with this novel combination therapy yielded results that were better than the known restenosis rates at 6 months with balloon angioplasty alone. Two patients had a Tosaka class I lesion, the remaining 8 were all Tosaka class III. All procedures were technically successful. No residual stenosis was seen angiographically. There were 2 cases of distal embolization (both in patients with a history of acute on chronic occlusion). Both could be treated successfully with aspiration embolectomy (n=2) and local (on-the-table) intra-arterial thrombolysis using a bolus of urokinase of 250,000 U (n=1). No access-site related complications were seen. Six patients had Duplex follow-up, one patient had an angiographic control (during angioplasty of an ipsilateral superficial femoral artery stenosis proximal of the treated segment a year after the index procedure), and the remaining 3 patients had clinical follow-up with ABI measurements. No TLR was performed. The clinical stage improved in all patients, with 9 patients becoming asymptomatic, and 1 patient having a Fontaine class IIa (Rutherford class 2). The patients that were evaluated with Duplex and/or angiography (n=7; mean follow-up 7 months) did not demonstrate any signs of neointimal hyperplasia. One patient underwent a (preplanned) toe amputation shortly after the revascularization procedure. No major-amputations or deaths occurred. The longer term follow-up of a larger cohort of 14 patients (10 female, 4 male) with clinically relevant (Rutherford 3–6) ISR who were treated with excimer laser angioplasty and drug-eluting balloons and a clinical follow-up of at least 9 months was evaluated, has been published, and it appears from this that the effect of laser debulking followed by DEB is sustained also at 2 years. The mean lesion length treated was 133.2±107.2 mm (range, 10 mm to 380 mm). The mean time to occurrence of restenosis after initial treatment was 8.6±4.7 months (range, 2 months to 18 months). Technical success was 100%. Distal embolization did not occur in any other patient, and thus remained
limited to the 2 cases described above. No other periprocedural major adverse events occurred.

All patients were available for clinical follow-up and 12 patients were available with Duplex follow-up. At a mean clinical follow-up of 19.1±8.7 months (range, 9 months to 38 months), 1 TLR was seen (at 3 years after the ISR treatment). In the patients with critical limb ischemia (n=7), no major amputations were needed. Duplex control (mean follow-up, 19.4±9.4 months; range, 9 months to 38 months) demonstrated a binary restenosis (>50%) in 1 case at 36 months. This was the same patient who had TLR. A 25% to 50% stenosis was seen in 4 patients (mean follow-up, 25 months; range, 19 months to 38 months). No signs of neointimal hyperplasia were demonstrated in 7 patients (mean follow-up, 14.3 months; range, 9 months to 19 months). The results with a mean clinical follow-up of 27.9 months±13.2 months (range 12 months to 54 months) have been presented during the 2015 CX symposium, and the results do not show any additional recurrences.

Similar good results were seen in a study that involved 48 patients who were randomly assigned to treatment using combination therapy of laser debulking and drug-eluting balloon angioplasty (n=24), or drug-eluting balloon angioplasty alone (n=24), with a follow-up to 12 months. All patients were suffering from chronic critical limb ischemia and presented with a total occlusion of the superficial femoral artery (Tosaka class III). Mean length of the treated stent was 20.0±10.1 cm in the combination therapy group and 23.3±9.1 cm in the DEB only group (P=NS). The treated lesion length was 22.4±9.4 cm vs 25.9±8.7 cm, respectively (P=NS). The occluded tract was limited to the stent only in 3 patients; in the remaining cases, stent obstruction was associated with proximal and/or distal thrombosis. Two cases of distal embolization were seen in the drug-eluting balloon group, and in 1 patient that was treated with combined therapy. The patency rates at 6 and 12 months in the combined therapy group (91.7% and 66.7%, respectively) were significantly higher than in the drug-eluting balloon group (58.3% and 37.5%, respectively; P=.01). TLR at 12 months was 16.7% in the combination therapy group, and 50% in the drug-eluting balloon angioplasty only group (P=.01). Also the number of major amputations was significantly reduced (8% vs 46%; P=.003). Ulcer healing was better in the patients that underwent combination therapy.

Further back-up for this approach comes from a study where positive results were obtained using directional atherectomy combined with DEB for debulking (keeping in mind the limitations of mechanical debulking as mentioned above).43,44

**SUMMARY**

Conventional balloon angioplasty, cutting balloon angioplasty, and cryoplasty do not provide a solution for ISR in the FP arteries. Drug-eluting balloon angioplasty provides good short-term results, but a late catch-up is seen for long lesions after 2 years and for all lesions after 3 years.

The burden of intima hyperplasia-associated ISR in the peripheral arteries is quite considerable, especially in long lesions, and therefore the use of debulking is essential. To obtain durable results, an approach of combining debulking with drug-eluting
balloons is necessary.

Class III lesions (total occlusions >5 cm) of the SFA are the most difficult to treat, because of the large amount of restenotic material that needs to be removed. Given the fact that the innermost layer of the substance that forms the ISR consists of noncellular material, the paclitaxel may not be able to reach the cellular (outermost) layer and cause a cytotoxic effect, and this explains the catch-up seen after 3 years when using drug-coated balloons as stand-alone therapy. Debulking offers the possibility to remove the smooth muscle cell inner intimal layer and the aqueous outer intimal layer that mainly consists of extra-cellular matrix, thus making the cellular component accessible for the action of drug-coated balloons.

**CONCLUSION**

In the treatment of ISR, debulking is probably key. There is a growing body of evidence that shows that by adding drug-eluting balloon angioplasty to debulking, results can be achieved that compare favorably to those described in the literature that were obtained with standard balloon angioplasty, cutting-balloon angioplasty, or debulking alone. Especially in long and complex lesions (Tosaka class III), this synergy is more pronounced, with currently no signs of late catch-up. Long-term follow-up and randomized studies are under way that will further define the role of combined excimer laser and drug-eluting balloon angioplasty in the treatment of ISR.

**REFERENCES**


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