Treating In-Stent Restenosis

Is laser atherectomy plus DCB the answer to achieving superior results in ISR treatment?

BY MICHAEL LICHTENBERG, MD

Technologies and techniques such as direct stenting have been developed to provide physicians with more options for the endovascular treatment of occlusive disease affecting the superficial femoral artery and infrapopliteal arteries. Stents allow physicians to deal with common procedural complications (eg, flow-limiting dissections). As a result of the more favorable outcomes that have been achieved, femoropopliteal stents are liberally implanted (> 400,000 annually worldwide)[1]; however, in spite of the overall trend toward decreasing the use of stents, femoropopliteal in-stent restenosis (ISR) remains a frequent and recurrent problem. Between 30% to 40% of patients will present with ISR after initial stent implantation and, of those, 65% will return with recurrent ISR after treament.[2] Along with current ISR solutions such as laser atherectomy, the development of drug-coated balloons (DCBs) has expanded the available treatment modalities. Additionally, the ability to potentially combine these treatments provides a new opportunity to improve outcomes in ISR.

Endovascular procedures such as balloon percutaneous transluminal angioplasty (PTA; with or without stenting) can produce trauma including vessel stretching, removal of endothelium, rupture of the internal elastic lamina, and medial injury. Vessel injury results in vessel recoil, negative remodeling, and development of neointimal hyperplasia. All of these processes continue to develop over time and eventually lead to the formation of a complex restenotic lesion with an underlying morphology that is distinct from de novo lesions.[3] ISR lesions are heterogeneous, consist primarily of a hydrated collagen matrix (60% to 80% of the restenotic volume is aqueous), and present a higher restenosis burden (Figure 1). Angiographic characteristics of femoropopliteal ISR lesions are also an important predictor of subsequent outcomes. Tosaka et al described angiographic patterns of ISR specific to the femoropopliteal segment: short, focal lesions (class I: ≤ 50 mm) and diffuse lesions (class II: > 50 mm) are associated with reasonable patency after treatment; however, total in-stent occlusions (class III) often predict recurrent ISR when treated with PTA (85% recurrence at 2 years).[2] This confirms the inadequacy of simple balloon dilation and the need for more advanced endovascular techniques. Additionally, removing as much of the stenosis as possible during the initial treatment of ISR may be an important step toward improving patency and reducing the risk of recurrent ISR.

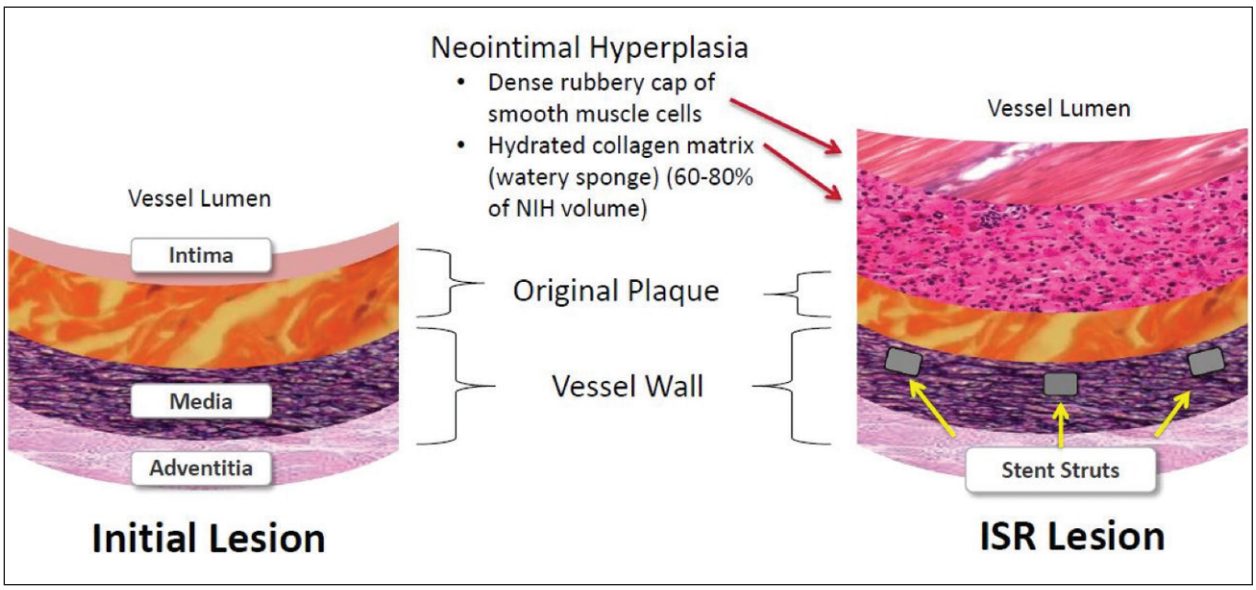

Figure 1. Morphology of ISR versus de novo lesions.

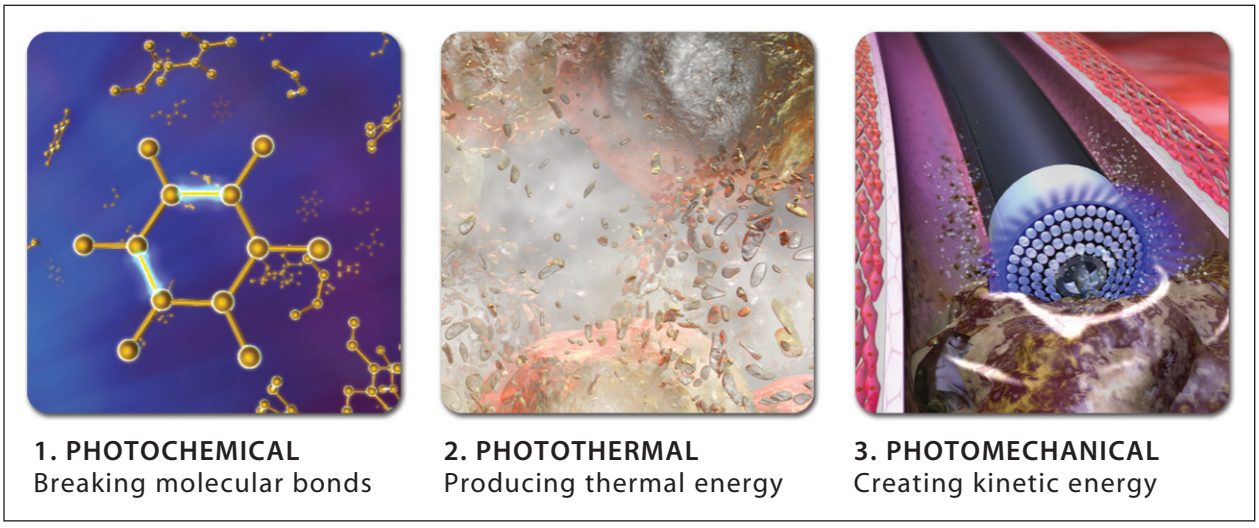

Figure 2. Excimer laser mechanisms of action.

USE OF LASER ATHERECTOMY IN TREATING ISR

Laser atherectomy works through photoablation, which is the use of light to break down and vaporize matter. Three distinct mechanisms of action contribute to laser photoablation (Figure 2) and the debulking/modification of plaque.

There are many unique benefits to the use of laser atherectomy in ISR, such as the ability to recanalize the vessel and debulk/modify plaque while avoiding interference with stent struts and reducing complications. Several studies support the safety and efficacy of the device in ISR, with results from the EXCITE ISR trial being the most recently published.

The EXCITE ISR trial was a prospective, multicenter, randomized study evaluating the effectiveness of an excimer laser with adjunctive PTA versus PTA alone for the treatment of femoropopliteal ISR.[4] The study enrolled 250 patients (169 laser plus PTA vs 81 PTA) with a mean lesion length of > 19 cm. Patients treated with laser plus PTA had superior procedural success (93.5% vs 81.7%), significantly fewer procedural complications including fewer dissections (7.7% vs 17.2%) and bailout stenting (5.3% vs 16%), greater freedom from target lesion revascularization (TLR) at 6 months (73.5% vs 51.8%), a 52% reduction in TLR (hazard ratio, 0.48; 95% confidence interval, 0.31–0.74), and a lower rate of major adverse events (5.8% vs 20.5%). Additionally, the benefits of laser plus PTA over PTA alone were proportionally better in longer lesions (> 25 cm). At 12 months, excimer laser atherectomy (ELA) and PTA was associated with a 43% reduction in TLR. Additionally, subanalysis of a subset of complex lesions (TASC C/D) revealed improved freedom from TLR at 12 months after treatment with ELA and PTA as compared with PTA alone (47% vs 24.5%; $P < .002$).[5] These data demonstrate that ELA and PTA is safer and more efficacious than PTA alone and highlights the ability of the excimer laser to improve outcomes in long, complex lesions. The ability of the laser to ablate and remove neointimal hyperplasia is ideally suited for the creation of a clean channel, which can accommodate subsequent complementary treatments as needed.

CASE STUDY

A 78-year-old man with in-stent occlusion of the right superficial femoral artery receives excimer laser debulking therapy with an adjunctive DCB (6 mm X 12 cm, Stellarex, Spectanetics Corporation) angioplasty (Figure 3).

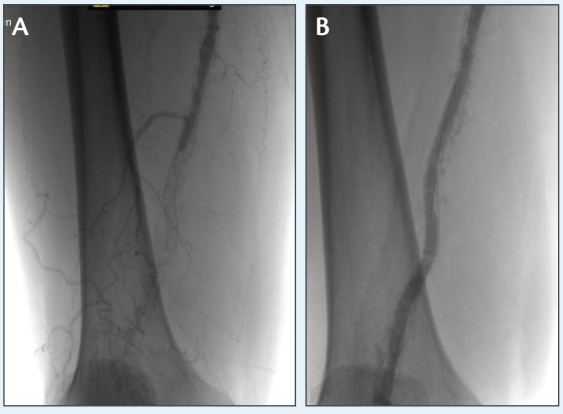

Figure 3. Prior to treatment (A). After laser and DCB treatment (B).

TABLE 1. OUTCOMES FOR LASER, DCBs, AND THE COMBINATION IN TREATING FEMOROPOPLITEAL ISR

Study (ordered by mean lesion length)	Treatment	Patients (n)	Lesions (n)	Lesion Length (cm)	Primary Patency			Freedom From TLR		
					6 months	12 months	24 months	6 months	12 months	24 months
FAIR[8]	PTA	57	57	8.1	55.3%	37.5%	–	81%	52.6%	–
	DCB	62	62	8.2	84.6%	70.5%	–	96.4%	90.8%	–
Virga/ Stabile[9,10]	DCB	39	39	8.3	–	92%	70.3%	–	92%	78.4%
DEBATE-ISR[11]	PTA	44	44	13.7	–	28%	–	–	69%	–
	DCB	42	42	13.2	–	81%	–	–	86%	–
van den Berg[12]	Laser + DCB	14	14	13.3	–	100%	91.7%	–	100%	92.9%
EXCITE ISR[4,5]	PTA	81	81	19.3	–	–	–	51.8%	41.7%	–
	Laser + PTA	169	169	19.6	–	–	–	73.5%	53.8%	–
Gandini[13]	DCB	24	24	23.3	58.3%	37.5%	–	–	50%	–
	Laser + DCB	24	24	20	91.7%	66.7%	–	–	83.3%	–

USE OF DCB IN TREATING ISR

DCBs have been well proven in short, femoropopliteal, de novo lesions with long-term patency.[6,7] Several studies have also evaluated the use of DCB in the treatment of superficial femoral artery ISR (Table 1).[4,5,8-13] However, not all ISR lesions are equal, and not all respond to treatment with DCBs evenly over the long-term. For example, a prospective noncontrolled study conducted by Virga et al[9] showed a 2-year patency rate of 70.3% and a 1-year patency rate of 92.1%, drawing into question the long-term effectiveness of DCB treatment in ISR. The DEBATE-ISR study is currently one of the only series to report safety and efficacy of DCBs in femoropopliteal ISR out to 3-year follow-up.[14] A benefit of DCB treatment in primary patency and freedom from TLR at 1- and 2-year follow-up was observed. However, a catch-up phenomenon was observed at 3 years, and the results demonstrated that treatment of more complex ISR lesions (Tosaka class III) was associated with an increased rate of TLR regardless of treatment with PTA or DCB. Although DCBs may provide an efficient treatment of short ISR lesions, they may lack long-term durability in more complex lesion subsets.

COMBINATION THERAPY (LASER PLUS DCB) IN TREATING ISR

Both DCB and laser show superiority to PTA at 1 year as stand-alone therapies; however, the benefit may be further improved overall, beyond 1 year and within complex subsets (occlusive/long ISR lesions). Recently, early results from a preclinical animal model of ISR chronic total occlusions demonstrated that laser debulking with adjunctive DCB produced overall better lumen quality compared to DCB alone.[15] The pilot study also showed that laser plus DCB resulted in a greater reduction in stenosis and intimal thickness, confirming the feasibility of successful DCB outcomes after revascularization with laser atherectomy. This interesting observation in animals is consistent with the available clinical data. For example, in a single-center, randomized trial of 48 patients, the combination of laser and DCB was compared to DCB alone in the treatment of complex ISR.[13] All of the patients had chronic limb ischemia and presented with long, occlusive, ISR lesions (> 20 mm; Tosaka class III). Along with improved primary patency in the laser plus DCB group (66.7%) versus DCBs alone (37.5%), the study demonstrated a significant reduction of TLR and major adverse events and improved wound healing at 12 months.

In a small case series of 14 patients (mean lesion length, 13.3 cm), van den Berg et al demonstrated the potential for the long-term durability of treatment with a laser in combination with DCB with patency rates of 100% and 91.7% at 1 and 2 years, respectively.[12] Additionally, the time to TLR after laser and DCB (one TLR event observed at 3 years) was significantly

better compared to initial treatment with PTA (mean time to TLR after PTA treatment was 8 months).

CONCLUSION

DCB angioplasty is an efficient treatment of short ISR lesions, but it may lack long-term durability in more complex lesion subsets. Early data suggest debulking and modifying the plaque before DCB treatment seems to be of key importance in more complex ISR lesions, such as Tosaka class II and III. Additionally, DCB application suffers from the same procedural limitations as PTA, including dissection and residual stenosis necessitating bailout stenting. As reported in EXCITE ISR, laser treatment provides a significant procedural advantage to PTA alone. Indeed, initial evidence suggests that laser plus DCBs is the right combination to achieve superior and more durable results in ISR treatment while avoiding additional stent layers, and the greatest benefits seem to be observed when the combination is applied in long, occlusive ISR lesions. ■

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Michael Lichtenberg, MD
Vascular Center Clinic
Arnsberg, Germany
M.Lichtenberg@klinikum-arnsberg.de
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