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What Does Histology Say About Vessel Preparation in Femoropopliteal ISR?

Initial pilot study results on laser revascularization with adjunctive DCB use.

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Peripheral artery disease (PAD) represents an advanced stage of atherosclerotic disease with an increasing prevalence, particularly in an aging population.[1] In regard to femoropopliteal disease, the most common location for occlusion is the superficial femoral artery (SFA), as it's uniquely one of the longest and most dynamically active vessels in the body, undergoing torsion, compression, flexion, and extension from hip and knee motion. Moreover, it has been reported that blood flow patterns associated with complex vascular geometry of the femoral artery is conducive to the development of atherosclerosis. Historically, the treatment of PAD was managed by medical therapy and open surgical bypass procedures.[2] Over the past decade, endovascular therapies including percutaneous transluminal angioplasty (PTA), stenting, and atherectomy, have evolved and become more widespread. However, endovascular procedures such as stenting invariably cause mechanical overstretch, resulting in endothelial denudation, plaque dissection, lesion protrusion into the lumen, rupture of the internal elastic lamina, and medial tears. Consequently, primary patency and clinical outcomes are dependent on the extent of vessel recoil with repair mechanisms that contribute to neointimal hyperplasia. The influence of these processes over time with continuous stress eventually lead to the formation of a complex in-stent restenotic (ISR) lesion with an underlying morphology that is distinct from de novo lesions.[3]

ISR lesions are heterogeneous and consist primarily of collagen types I and III along with varying amounts of proteoglycans and smooth muscle cells (60%–80% of the restenotic volume is aqueous), resulting in a high restenosis burden. A variety of factors contribute to the development of SFA ISR (Figure 1). Angiographic characteristics of femoropopliteal ISR lesions are also an important predictor of subsequent outcomes. Tosaka et al[4] described angiographic patterns of ISR specific to the femoropopliteal segment:

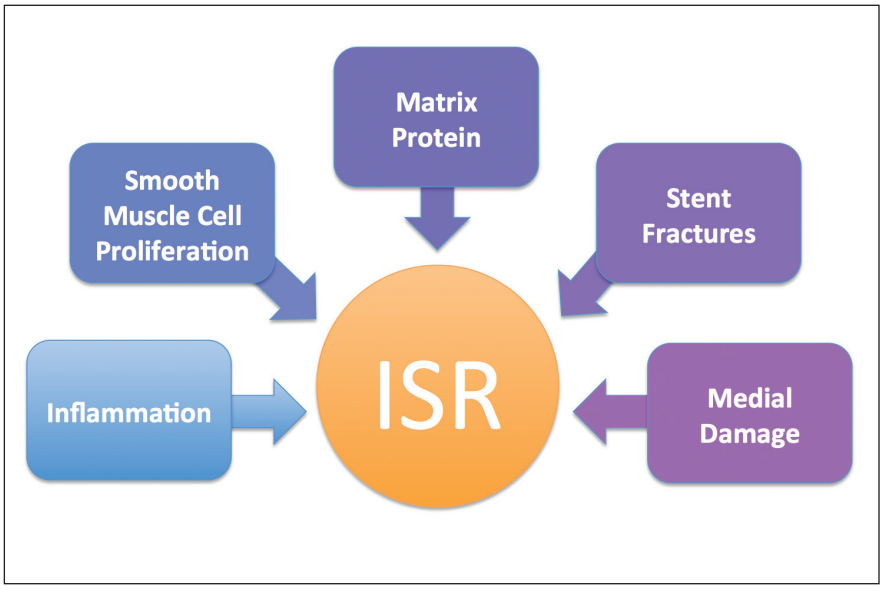

Figure 1. Factors contributing to ISR.

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TABLE 1. HISTOMORPHOMETRY 28 DAYS AFTER TREATMENT (120D IN FIGURE 2)

	Sections	Lumen Area (mm^2)	Neointimal Area (mm^2)	Stenosis (%)	Neointimal Thickness (mm)
PTA + DCB	6	2.91 ± 0.58	2.82 ± 0.3	49.59 ± 6.74	0.35 ± 0.05
Laser + DCB	12	3.60 ± 0.94	2.36 ± 0.54	40.27 ± 11.50	0.21 ± 0.12
P value	–	.060	.036*	.044*	.012*

Abbreviations: DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty.
*Significant based on one-tailed t-test ($P < .05$).

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).[4] Approximately one-third of ISR lesions are class III total occlusions,[4,5] confirming the inadequacy of simple balloon dilation (angioplasty) and the need for more advanced endovascular techniques in this complex subset of lesions.

ESTABLISHING A TRANSLATIONAL MODEL TO ASSESS ISR-CTO TREATMENTS

Currently, there is no reliable translational ISR-chronic total occlusion (CTO) model to assess endovascular devices and treatments. An ISR model in the carotid artery of hypercholesterolemic rabbits was established after stent overstretch and bovine thrombin injections to create CTOs (Figure 2), thereby mimicking class III-type lesions in humans. The composition of the matured thrombus within the stent mass is mainly derived from dense to loosely packed smooth muscle cells within a proteoglycan matrix, scattered nonfoamy macrophages, and varying degrees of angiogenesis, similar to what has been observed in human ISR lesions/total occlusions. The creation of this animal model of ISR-CTO allows for pilot studies to explore the potential benefits of new technologies, such as drug-coated balloons (DCBs), that are currently not approved for use in human ISR in the United States. The objective of our pilot study was to assess the early outcomes of laser debulking with adjunctive DCB (n = 4) compared with standard PTA and DCB (n = 3) in a rabbit model of ISR CTO.

Figure 2

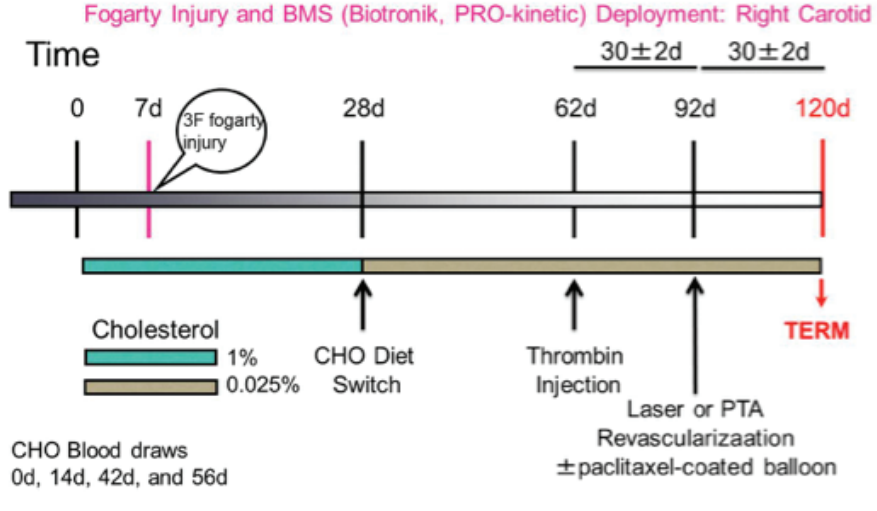

Figure 2. Experimental design, animal model of ISR-CTO. The study lasted for a total of 120 days. Animals were fed a 1% high-cholesterol diet (0–28d; CHO) with subsequent 3-F Fogarty-induced vascular injury and bare-metal stent implantation after 7 days (7d). The atherogenic high-cholesterol diet was continued until day 28 (28d), at which time the diet was switched to 0.025% cholesterol for the remainder of the study. An intraluminal bovine thrombin injection was performed at 62 days (62d) after initiation of the CHO diet to create the total occlusion. Thirty days after thrombin injection, animals underwent endovascular treatment (92d). Final follow-up results were obtained 28 days after treatment (120d).

Persistent in-stent total occlusion at the time of the

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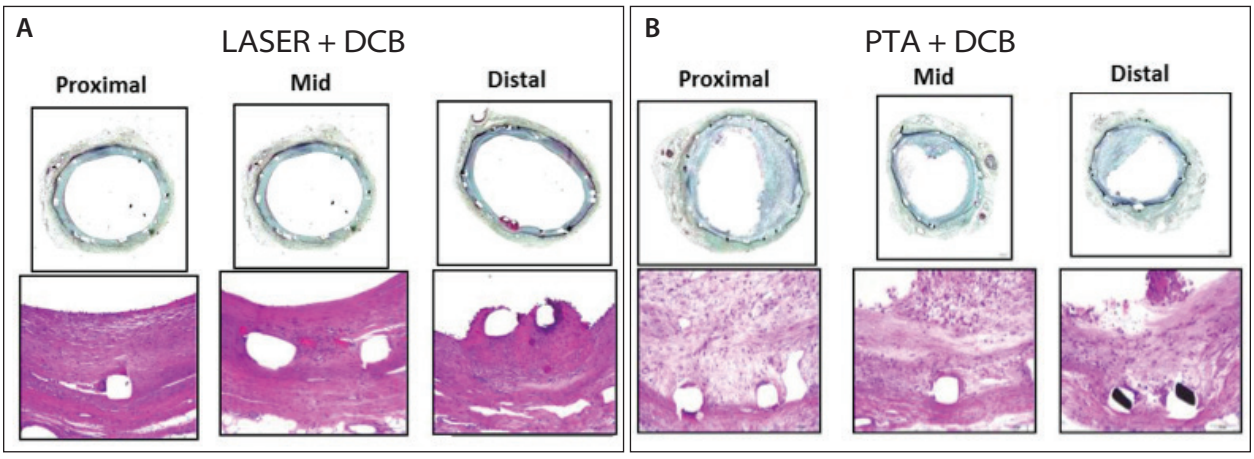

Figure 3. Selected in-stent histomorphology 28 days after treatment (120d in Figure 2). Laser and DCB, the stent remains widely patent 28 days after treatment (A). PTA and DCB, the stent remains occluded 28 days after treatment (B).

endovascular intervention (Figure 2, 92d) was noted in seven of eight arteries. Of the vessels that were occluded at treatment, 75% of laser and DCB vessels (3 of 4) versus 0% (0 of 2) PTA and DCB–treated vessels remained patent at 28-day postintervention follow-up (Figure 2; 120d). The PTA and DCB group exhibited an unhealed luminal surface with exposed plaque material consisting mainly of macrophage-derived foam cells and focal platelets/fibrin with incomplete endothelium while the laser and DCB treatment showed focal fibrin deposition and/or inflammatory cell aggregates admixed with fibrin, whereby stent struts were covered by a thin neointimal layer. Laser debulking with adjunct paclitaxel DCB in established CTOs in the animal model produced overall better lumen quality, reduced stenosis, and lessened intimal thickness at 28 days after treatment compared to PTA and DCB (Table 1; Figure 3).

CONCLUSIONS

The management of ISR can be very challenging and may require repeated interventions. This pilot study confirms the feasibility and successful outcome of laser revascularization with DCB adjunctive in a rabbit carotid artery in-stent total occlusion model. ■

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