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ENDOVASCULAR TECHNIQUES IN LIMB SALVAGE: CUTTING, CRYO, BRACHY, AND DRUG-ELUTING BALLOONS

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Abstract

The complex pathophysiology response to injury of the lower-extremity arteries has prompted the development of several unique balloon technologies to overcome initial technical failures and short-term intimal hyperplasia. Cryoplasty alters the cellular and mechanical properties of the vessel wall during angioplasty. Cutting balloons incise the wall, preventing elastic recoil and allowing expansion of the lumen at a lower pressure, thus limiting barotrauma. Drug-eluting balloons actively transfer inhibitory compounds to the wall during the initial therapy, while brachytherapy balloons allow for localized delivery of radiation to inhibit the proliferative response seen after angioplasty. These platforms provide unique means to enhance immediate and short-term results and also reduce stent usage in the lower extremity.

Introduction

Percutaneous approaches to the lower extremity have expanded considerably in recent years. As the boundaries of therapy have advanced, so have the shortcomings of percutaneous transluminal angioplasty (PTA) in complex lesions, which uses the pressure of a balloon to dilate a stenotic segment in a vessel (Figure 1). PTA can involve several initial technical complications, such as flow-limiting dissection leading to occlusion or elastic recoil leading to technical failure; it also has a high short-term restenosis rate due to negative remodeling and neointimal proliferation. While the development of stent technology has sought to address these two major concerns, several new balloon angioplasty systems based on innovative, disruptive technology have emerged, combining the features of conventional balloon dilation with advanced physical, microsurgical, and pharmacological capabilities. Based on a controlled and less barotraumatic dilation of the lesion, cryo- and cutting-balloon angioplasty have the potential to improve the immediate and short-term outcomes of catheter-based therapy. Brachytherapy balloons deliver local radiotherapy, whereas drug-eluting balloons deliver high drug concentrations to the angioplasty site and are designed to impede early restenosis by reducing local cellular proliferation. This article will review these new balloon technologies and their results in the lower extremity.

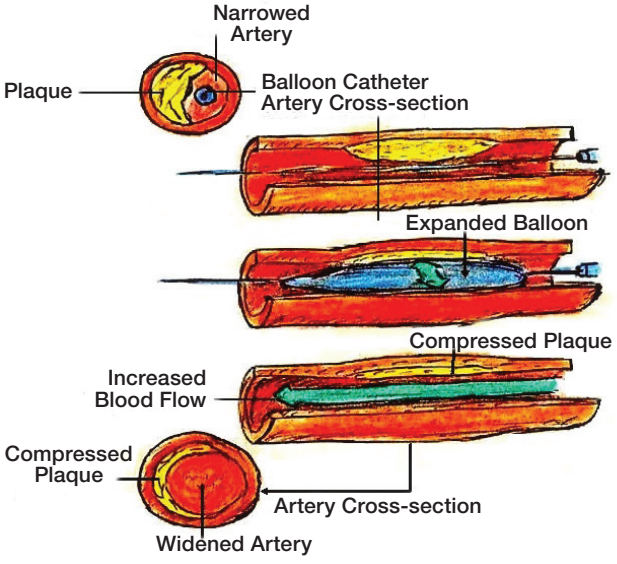

Figure 1. Illustration of a percutaneous transluminal angioplasty (PTA) balloon catheter that delivers a specified pressure against the vessel wall to dilate a stenotic segment in a vessel. PTA induces vessel wall disruption leading to a controlled dissection of the layers in most circumstances. Redrawn after Cardiology Associates of Derby, http://www.cardio-assoc.com/services-angio.html.

Cutting Balloons

Cutting balloons (CB) are low-pressure balloon catheters that have three or four microsurgical blades mounted longitudinally on the balloon or an elliptical blade that can cut directly into the vessel wall during initial balloon inflation (Figure 2). They exert 8 atm of pressure. Cutting the vessel and inducing a controlled disruption of the internal elastic lamina induces mechanical and biological effects to reduce elastic recoil, vessel wall injury, and

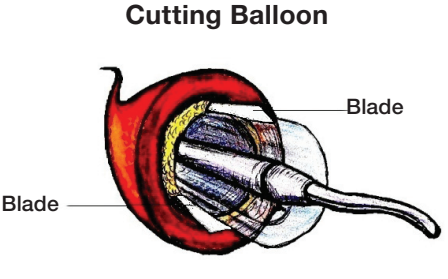

Figure 2. Illustration of a cutting balloon catheter that has three or four microsurgical blades mounted longitudinally on the balloon or an elliptical blade that directly cuts into the vessel wall during initial balloon inflation, producing defined disruption lines.

potentially restenosis.[1] Compared to PTA, CB-PTA has shown to be effective in decreasing the inflammatory response, endothelial damage, and vascular smooth muscle cell proliferative response and allows larger lumen areas to be achieved.[1]

A few studies have reported the results of CB-PTA for infrainguinal de novo arterial stenosis. Rabbi et al. reported a series of 11 patients and showed a primary angiographic success rate for CB-PTA of 90.9%, a primary patency rate at 3 months of 88%, and 100% of threatened limbs salvaged.[2] In a report of predominantly noncomplex femoropopliteal lesions, Branchereau and his colleagues demonstrated an overall technical success rate of 96.3% and a complication rate of 8.9%.[3] The primary patency rate was 82.1% at 12 and 24 months in patients with claudication (femoropopliteal lesions). The 1- and 2-year results for femoropopliteal and infrapopliteal lesions in patients with critical limb ischemia (CLI) were as follows: primary patency, 64.4% and 51.9%; limb salvage, 84.2% and 76.9%; and survival, 92.6% and 88.5%, respectively. More distal lesions and TASC (Trans-Atlantic Inter-Society Consensus) classification were significant independent risk factors for outcome ($P < .05$). Treatment of multiple segment lesions was an independent predictor of a favorable outcome ($P = .04$). Ansel et al. reported procedural outcomes at a mean of 1 year of follow-up in 73 patients with symptomatic lower limb ischemia and demonstrated that 89.5% of threatened limbs were salvaged.[4] Amighi et al. reported the results of a randomized controlled trial (RCT) comparing PTA and CB-PTA in the femoropopliteal arterial lesions, and CB-PTA did not prove to be superior to conventional PTA.[5] More distal lesions and TASC type C or D lesions were significant independent predictors of worse long-term results following CB-PTA.[5] In the Restenosis Cutting Balloon Evaluation Trial (RESCUT),[6] a multicenter European RCT, 428 patients with in-stent restenosis were randomized to CB versus angioplasty. At the 7-month angiographic follow-up, the binary restenosis rate was not different between the groups and showed a similar pattern of recurrent restenosis. CB-PTA appears to be appropriate for restenotic lesions in vein grafts where the fibrotic nature of the lesion lends itself to cutting and dilations. Multiple reports have shown very good outcomes following CB-PTA of stenotic lesions in infrainguinal vein grafts.[7-9] CB-PTA has not been widely accepted as a primary tool for lower extremity interventions.

Cryo Balloons

Cryoplasty (CP) combines conventional low-pressure balloon angioplasty with application of cryotherapy (30-second cooling of the vessel to -10°C) (Figure 3). Cryotherapy is thought to create a uniform rigidity in the wall, to alter collagen fibrils, and to induce smooth muscle cell apoptosis; this produces a uniform mechanical load on the balloon vessel wall interface that will decrease significant plaque dissection, limit recoil in the vessel, and decrease intimal hyperplasia.[10] The single cryoplasty system on the market at present uses a double-balloon system that exerts 8 atm on the lesion and is accompanied by cold-induced injury to the wall. The cryoplasty modality uses less pressure than standard balloon angioplasty (8 atm rather than 15 atm) and transiently cools the vessel wall to -10°C. Cryoplasty appears to achieve its best results in femoropopliteal stenoses and occlusions <10 cm in length.[11] The final results of the cryoplasty safety registry of noncomplex femoropopliteal lesions have shown a primary patency of 82% at 10 months in 102 patients.[12, 13] There appears to be a lower dissection rate with cryoplasty compared to conventional PTA. The mode of failure in cryoplasty was different, with stenosis being more common than occlusion, and this suggests that the modality alters the biology of healing in the vessels.[14]

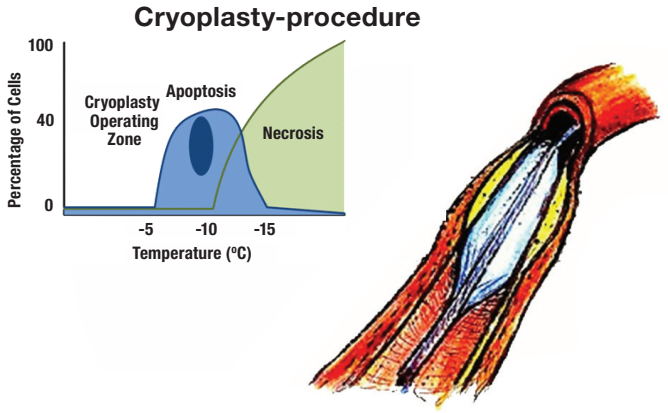

Figure 3. Illustration of a conventional low-pressure balloon angioplasty with a compartment that allows cryotherapy (30-second cooling of the vessel to -10°C), which alters the mechanical and biological properties of the vessel. Inset redrawn after: Tatsutani KN et al. In vitro evaluation of vascular endothelial and smooth muscle cell survival and apoptosis in response to hypothermia and freezing. Cryo Letters. 2005 Jan-Feb;26(1):55-64.

Reports have shown that there is a significant decrease in adjuvant stent utilization in the cryoplasty group, and this has been seen in other studies, most of which did not include predominantly complex superficial femoral artery (SFA) lesions.[12-14] The COLD study evaluated the safety and efficacy of cryoplasty versus conventional angioplasty for focal popliteal arterial occlusive disease and demonstrated that cryoplasty of the popliteal artery alone showed a lower anatomic success when compared with conventional PTA.[15] In a study investigating the immediate and long-term results of cryoplasty versus conventional balloon angioplasty in the femoropopliteal artery of diabetic patients, Spiliopoulos et al. demonstrated that cryoplasty was associated with lower primary patency and more clinically driven repeat procedures after long-term follow-up compared with conventional balloon angioplasty.[16] The BTK-CHILL study demonstrated that cryoplasty therapy is a safe and effective method of treating infrapopliteal disease[17] while the CLIMB registry demonstrated equivalence to conventional PTA, especially for shorter infrapopliteal lesions (<50.0 mm).[18] Controversies continue to exist on the cost benefit of cryoplasty versus conventional PTA.[14, 19, 20] Cryoplasty appears to be an appropriate therapy for noncomplex infrainguinal lesions and is equivalent to conventional PTA.

Brachytherapy Balloons

Two forms of radiation—gamma and beta—are commonly used for intravascular balloon therapy (IVBT), and both have limitations when used in peripheral vessels.[21] Beta sources produce high-energy particles that rapidly lose activity over short distances, resulting in limited penetration. Thus, for the entire artery wall to be exposed to an equal dose, the radiation source must be centered in the lumen of the vessel. When a gamma source is used, there is complete penetration of the wall to beyond the adventitia, which reduces the required delivery precision compared with beta radiation. Gamma radiation also requires more elaborate and costly radiation protection measures for the operators. Both types of radiation can be delivered by either the intravascular insertion of a catheter containing the radiation source in a balloon (beads, gel, liquid) or by a wire source, where the tip of the wire is radioactive (Figure 4). These sources are placed in the target vessel for a calculated period of time.[22]

Delivery of radiation to the injured field in a vessel has had beneficial effects. Gamma radiation has induced positive vascular remodeling after balloon angioplasty in a prospective randomized

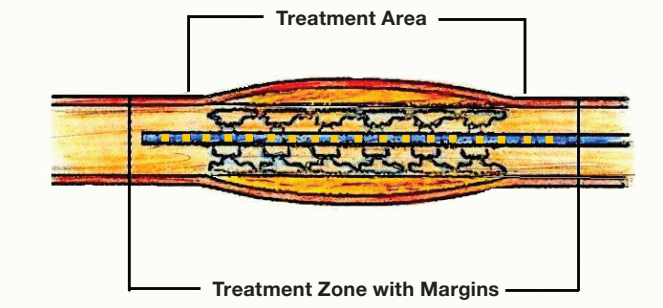

Figure 4. Illustration of a brachytherapy catheter. The radiation source can be delivered by either the intravascular insertion of a catheter containing the radiation source in a balloon (beads, gel, liquid) or by advancement of a wire where the tip is the radioactive source to allow it to lay at the balloon position. Redrawn after Radiology Associates of Hollywood, http://rahradiationoncology.com/serv-ivb.htm.

intravascular ultrasound (IVUS) scan study.[23] When doses of 12-14 Gy (gamma radiation) are applied endoluminally to the femoropopliteal segment after PTA, there is a two-fold increase in 12-month patency compared to untreated controls.[24-26] Similar results were noted in the PARIS trial.[27] In a recent study where PTA was performed with and without brachytherapy, magnetic resonance imaging (MRI) showed that brachytherapy decreases luminal loss due to inward vessel remodeling but compromises healing of the disrupted vessel surface.[28] Endovascular radiotherapy can prevent intimal hyperplasia after stent implantation in femoropopliteal arteries.[29]

Drug-Eluting Balloons

Nonstent-based local drug delivery has three potential advantages: (1) homogenous drug transfer to the vessel wall; (2) highest drug concentrations at the vessel wall at the time of injury; and (3) absence of a stent or delivery polymer. Generally, a conventional balloon angioplasty is done before using a coated balloon. When a coated balloon is used, the 1-minute inflation time allows the diffusion of 6% of the drug embedded on the balloon into the tissue (Figure 5). Of the original dose, 4% will be retained on the surface of the balloon and 90% will be lost in the bloodstream.[30]

In the THUNDER (local Taxan with sHort time exposure for redUctioN of restenosis in Distal artERies) multicenter trial, Tepe et al.[31] randomly assigned 154 patients with stenosis or occlusion of a femoropopliteal artery to treatment with standard balloon catheters coated with paclitaxel, uncoated balloons with paclitaxel

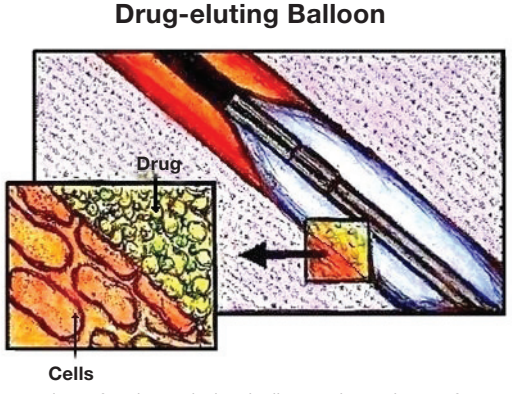

Figure 5. Illustration of a drug-eluting balloon where the surface of the balloon is covered in a polymer that allows direct vessel wall delivery of a drug. A one-minute inflation time allows the diffusion of 6% of the drug embedded on the balloon into the tissue.

dissolved in the contrast medium, or uncoated balloons without paclitaxel (control). The primary endpoint was late lumen loss at 6 months. The authors reported no adverse events attributable to the paclitaxel-coated balloons. At 6 months, the mean late lumen loss was 1.7 ± 1.8 mm in the control group, 0.4 ± 1.2 mm (P <.001) in the group treated with paclitaxel-coated balloons, and 2.2 ± 1.6 mm (P = .11) in the group treated with paclitaxel in the contrast medium.

In the FemPac (Femoral Paclitaxel) pilot trial, Werk et al.[32] randomly assigned 87 patients with femoropopliteal peripheral artery disease to percutaneous intervention with uncoated or paclitaxel-coated balloon catheters. The primary endpoint of angiographic late lumen loss at 6 months was significantly reduced in patients treated with the paclitaxel-coated balloon, although this angiographic primary endpoint was obtained only in 31 of the 45 patients treated with the paclitaxel-coated balloon. Patients treated with the paclitaxel-coated balloon also had a significant reduction in target lesion revascularization at 6 months, which was maintained up to 24 months.

The LEVANT I trial randomized 101 patients to either drug-eluting balloon or standard angioplasty for the treatment of diseased femoropopliteal arteries, and it demonstrated similar effects to the other trials.[30] LEVANT II will randomize approximately 476 patients using a similar therapeutic strategy and will follow them for 5 years. The PICOLLO and PADI trials are ongoing randomized trials comparing the angiographic outcome of paclitaxel-coated balloons with plain balloon angioplasty in treating below-the-knee lesions.[33, 34] Most recently, the PACIFIER Study aims to randomize patients with superficial femoral or popliteal artery disease to paclitaxel-coated or uncoated conventional balloon groups. Results to date of drug-eluting balloons are promising, and their role in infrainguinal disease will be recognized as the clinical trial data accumulates.

Conclusion

Advanced balloon angioplasty systems are evolving and are capable of adapting to the relatively hostile physical and hemodynamic environment of the lower extremity. All are targeted at controlling either immediate technical failures or short-term restenosis. Cutting and cryoballoon angioplasty are currently available for clinical use for recalcitrant lesions. Brachytherapy and drug-eluting balloons remain in the research domain. The cost benefit of each remains to be determined, and thus their future role in revascularization strategies will be based on their short- and long-term efficacy.

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Keywords: balloon angioplasty, brachytherapy balloon, critical limb ischemia, cryoplasty, cutting balloon, drug-eluting balloon, lower extremity intervention, percutaneous transluminal angioplasty, restenosis

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