Endovascular Treatments for Critical Limb Ischemia

The past, present, and future of treating this disease.

BY JEFFREY H. FREIHAGE, MD, AND ROBERT S. DIETER, MD, RVT

Critical limb ischemia (CLI) generally manifests from advanced, multilevel atherosclerotic disease of the lower-extremity vasculature. Strictly speaking, CLI is defined as the presence of rest pain, nonhealing ulceration or gangrene, plus objective evidence of diffuse pedal ischemia (Fontaine classes III and IV or Rutherford categories 4, 5, or 6) (Table 1).[1-3] To be considered CLI, rest pain, in the absence of tissue loss, should persist at a level that requires moderate-to-strong analgesia for at least 3 weeks. Without revascularization, patients with Rutherford 5 or 6 CLI symptoms are at a significant risk for limb loss, as evidenced by 95% 1-year major amputation rate.[4] Furthermore, the 30-day mortality and morbidity rates associated with a major amputation in Rutherford category 5 and 6 patients are up to 30% and 37%, respectively.[5] However, some studies have shown that limb salvage has proven to improve survival relative to those requiring amputation (60% vs 26% at 5 years for limb salvage patients and amputees, respectively).[6] In addition to the mortality benefit, limb salvage has proven to lower overall health care costs and improve the patient's quality of life.[7,8] For these reasons, limb salvage in CLI is a noble endeavor worthy of physician efforts and health care resources.

Figure 1. Angiography of the right anterior tibial artery in a patient with CLI. Before balloon angioplasty (A). Initial result after balloon angioplasty (B).

Surgical bypass has historically been the gold standard for treatment of CLI. Surgical data have demonstrated excellent long-term patency and clinical durability, as well as a 5-year limb salvage rate approaching 80%.[9-12] However, the associated mortality (≤6%) and morbidity rates (wound infection 30%, graft infection 1.5%, myocardial ischemia 3%, and graft stenosis/occlusion 15% to 30%) of surgical bypass in CLI patients can be prohibitive.[13-15] Furthermore, many patients have poor distal target vessels and lack suitable veins due to previous coronary artery bypass grafts or vascular surgery. For these reasons, there is a strong interest in the further development of endovascular therapies for CLI. Also, if a surgical bypass graft acutely fails, often the limb becomes acutely threatened; this is not the case in endovascular failure.

Most patients with CLI have chronic diffuse and obstructive atherosclerosis involving the infrapopliteal arteries. The attainment of limb salvage in CLI relies on the restoration of straight in-line flow within at least one of the tibial vessels to meet the increased metabolic demands of wound healing. Although improvement in

TABLE 1. CLASSIFICATION OF PERIPHERAL ARTERIAL DISEASE

Fontaine Stage	Rutherford Category	Clinical	Objective
I	0	Asymptomatic	Normal treadmill or reactive hyperemia test
IIa	1	Mild claudication	Normal treadmill or reactive hyperemia test
IIb	2	Moderate claudication	Completes treadmill exercise, AP after exercise >50 mm Hg, but >20 mm Hg lower than resting value
IIb	3	Severe claudication	Completes treadmill exercise, AP after exercise >50 mm Hg, but >20 mm Hg lower than resting value
III	4	Ischemic rest pain	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile, TP <40 mm Hg
IV	5	Minor tissue loss	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile, TP <40 mm Hg
IV	6	Ulceration or gangrene	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile, TP <40 mm Hg

AP=ankle pressure; PVR=pulse volume recording; TP=toe pressure.
Treadmill protocol to be 2 miles per hour, 12% grade.

blood flow may be only temporary due to graft failure in surgical cases or restenosis in endovascular therapies, limb salvage may still be accomplished because less blood flow is required for maintenance of tissue integrity once wound healing has occurred.[16]

Evidence supporting endovascular techniques as first-line therapy is accumulating.[17] The improvements in equipment and technique have expanded the application of endovascular therapies to patient groups with more extensive and difficult-to-treat lesions. We review the existing data, ongoing trials, and future developments in endovascular therapy and techniques (Table 2) for the treatment of CLI.

TABLE 2. ENDOVASCULAR TECHNIQUES

- Balloon angioplasty
- Stenting
  - Bare-metal stents
  - Drug-eluting stents
- Excisional atherectomy
- Cryoplasty
- Excimer laser
- Cutting Balloon

ENDOVASCULAR TECHNIQUES

Balloon Angioplasty

Primary balloon angioplasty (BA) has been used as the main endovascular revascularization modality in CLI (Figure 1). Patients with CLI of the lower extremity typically have multiple stenotic lesions and occlusions along the arterial tree from the superficial femoral artery to the pedal arch.[15] Because of the existence of diffusely obstructive disease within the infrapopliteal arteries in most patients, dilatation of proximal lesions (above the knee) is often not sufficient for limb salvage. Rather, restoration of straight in-line flow to the pedal arch in one or more of the tibial arteries is necessary for clinical success. The availability of fine guidewires, lower-profile balloons, and improved catheters, along with increased operator experience, has led to improvement in both technical and clinical outcomes of BA in patients with CLI.

In a nonrandomized series of 270 patients (284 limbs) with CLI, Dorros et al reported technical success in 91% of lesions with BA (98% in stenotic lesions and 73% in occlusions) of the tibioperoneal vessels.[18] In this series, 95% of CLI patients had clinical improvement at the time of discharge with a low procedure-related mortality rate (.4%). The long-term follow-up of this patient series revealed an impressive 5-year limb salvage rate of 91%.[19] Eight percent of limbs required surgical bypass by year 5 for salvage, and major amputations occurred in 9% of

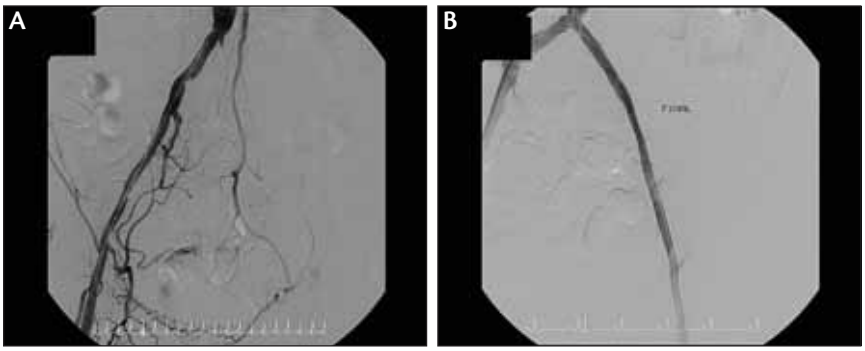

Figure 2. Angiography of the left common iliac artery in a patient with CLI. Before intervention, the patient had total occlusion of the vessel (A). After stent placement (B).

limbs. Patients with Rutherford category 3 symptoms at presentation required significantly less surgical bypass or amputation than those with Rutherford category 4 symptoms. Multiple other case series have reproduced similar technical success rate of BA in CLI.[20-22] In a series by Brillu et al, the technical success rate of 94.5% with an associated limb salvage rates of 86% at 2 years led the investigators to conclude that BA should be the initial treatment for patients presenting with CLI.[23] In a 10-year report of CLI outcomes by Kudo et al, the technical success rate was 96.4% with a 5-year limb salvage rate of 89.1%.[24] Compared to a surgical approach, BA appeared to result in better outflow revascularization with a significant improvement in distal extremity perfusion, immediate relief of rest pain, and augmentation of ulcer healing.

Although numerous case series provided compelling evidence that BA produced similar clinical outcomes with less morbidity than bypass surgery, randomized prospective data were lacking. The BASIL trial was conducted to compare the outcome of bypass surgery and BA in patients with CLI.[17] Four-hundred fifty-two patients with infrainguinal CLI were randomly assigned to either a surgery-first or an angioplasty-first strategy to compare major amputation-free survival rates between the two strategies. For a patient to be enrolled, disease that was amenable to both surgery and angioplasty was required. During the audit phase of the study, only 29% of potentially eligible patients were suitable for randomization. For technical reasons, 16% of patients were not angioplasty candidates, whereas 20% were not deemed surgical candidates. Although 30-day mortality rates were statistically equivalent between surgery and angioplasty (5% and 3%, respectively), complications were significantly less in the angioplasty arm. Furthermore, clinical success at 1 year was not statistically different between surgery and angioplasty (56% vs 50%, respectively). Cost analysis demonstrated that in the first 12 months, surgery was about one-third more expensive than angioplasty. The study concluded that both a bypass-first and an angioplasty-first approach are acceptable in patients with CLI. However, surgery is more costly with a higher complication rate in the first 30 days.

Unfortunately, BA alone can lead to a technically suboptimal result due to vessel recoil, lesion length >10 cm, heavy calcification, intimal dissection, total vessel occlusion, or an inability to pass the wire distal to the lesion. In these circumstances, other techniques may be required to attain sufficient flow for wound healing. In one series, cutting balloon use in the infrapopliteal arteries was associated with a 20% rate of intimal dissection resulting in an inadequate hemodynamic result and a need for adjunctive stenting.[25] Thus, cutting balloons should be reserved for niche uses, such as ostial lesions or lesions due to neointimal hyperplasia.

In cases in which the wire is unable to be passed distal to the lesion, reports of successful revascularization with subintimal angioplasty[26,27] and also retrograde tibial access[28] have been utilized with similar clinical results as other BA trials. Ingle et al reported technical success in 86% of the 67 consecutive patients in whom subintimal angioplasty was attempted.[26] These results translated into a 36-month limb salvage rate of 94% by life-table analysis. The data on other techniques used to complement BA will be discussed in the following sections.

Stenting

Implantation of stents, either balloon-expandable or self-expanding, in the iliac and femoral arteries is common practice to relieve symptoms related to hemodynamically significant lesions in these arteries (Figure 2). However, due to the diffuse nature of the disease process in CLI, it is rarely acceptable to address only proximal lesions without restoring flow within at least one tibial vessel. Data regarding the use of stents in the infrapopliteal arteries are limited. The most common reasons to use stents in arteries below the knee are flow-limiting dissections and vascular recoil. In one series of 82 patients (92 limbs), of whom 68% had CLI, technical success was achieved in 94% of lesions.[29] Furthermore, clinical success at 1 year was seen in 96% of patients with CLI who underwent successful intervention. XCELL is an ongoing single-arm registry study expected to enroll 140 CLI patients treated by primary infrapopliteal vessel stenting using the Xpert (Abbott Vascular, Santa Clara, CA) nitinol stent. This reg-

istry protocol requires follow-up angiography at 12 months with a primary endpoint of 12-month amputation-free survival.

Due to the successful inhibition of neointimal hyperplasia by sirolimus-eluting stents (SESs) in the coronary vasculature, Siablis et al compared SESs to bare-metal stents (BMSs) in infrapopliteal artery lesions in the CLI population.[30] In this nonrandomized prospective single-center study, 6-month angiographic and clinical results were compared among 29 patients (65 lesions) who received BMSs and another 29 patients (66 lesions) who received SESs for bailout after suboptimal BA. Although limb salvage was 100% in both groups, the use of SESs was associated with an improved 6-month patency rate (92% vs 68%, respectively; *P*=.002). This difference was associated with a statistically significant reduction of target vessel revascularization at 6 months. Further studies are needed to determine if improvement in 6-month patency and the decreased need for target vessel revascularization led to improved long-term clinical outcomes.

> "Endovascular therapies do not jeopardize distal target vessels if surgery is considered at a later date."

Future technology may address the problem of restenosis in the lower extremity by the use of bioabsorbable stents with drug-eluting capability.[31] In a case series of 20 patients with CLI treated with absorbable-metal stents in the infrapopliteal arteries by Bosiers et al, technical success was accomplished in all 20 patients (100%). At 12 months, the primary patency rate was 78.9% with limb salvage of 94.7%. Furthermore, histologic analysis demonstrated progressive stent degradation during the first year after implantation. However, randomized data are needed to determine if bioabsorbable stents lead to better clinical outcomes than either BA or other forms of stenting.[32]

Excimer Laser Therapy

Via a flexible fiber optic catheter, the excimer laser delivers intense ultraviolet energy in short pulses. Plaque removal is accomplished by photoacoustic ablation, theoretically reducing the potential for embolic complications with minimal thermal injury to the surrounding tissues. One advantage of the laser is that it may facilitate recanalization of chronic occlusions in which the wire is unable to be passed. In complete occlusions, the stepwise technique allows probing of the wire at the occlusion stump and advancement of the laser past the wire to create a lumen within the vessel; this may serve as an alternative to subintimal or other chronic total occlusion techniques.

The LACI (Laser Angioplasty for Critical Limb Ischemia) trial was a prospective, multicenter registry conducted to evaluate the effectiveness of excimer laser-assisted angioplasty in CLI patients with complex femoropopliteal and tibioperoneal occlusive disease who were poor surgical candidates.[33] In this study of 145 patients (155 limbs), 92% of patients had total occlusions of the limb, with a mean lesion length of 16.2 cm. Procedural success (<50% residual stenosis) was 86% with a 6-month limb-salvage rate of 93% of limbs. Of note, 96% of patients required adjunctive balloon angioplasty, and 45% of patients required stent implantation. Similar results were reported in the smaller LACI Belgium and the Cardiovascular Institute of the South "LACI Equivalent" studies.[34,35] Although results of LACI are comparable to the case series of BA in CLI, no randomized data comparing outcomes or cost effectiveness of excimer laser therapy to balloon angioplasty exist. The laser is rarely used as a stand-alone device due to the relatively small diameter of the catheter.

Excisional Atherectomy

The SilverHawk (FoxHollow Technologies, Redwood City, CA) is an excisional atherectomy device, which theoretically allows for greater luminal gain with less plaque displacement and barotrauma. SilverHawk is promoted as a stand-alone therapy without the need for adjunctive angioplasty or stenting. In a prospective evaluation by Kandzari et al, use of the device in the setting of CLI resulted in a 99% procedural success rate in the 76 limbs that underwent intervention.[36] In this study, 40% of the lesions were in the tibioperoneal vessels or pedal arteries. At 6 months, 82% of the patients were either amputation free or had a less-extensive amputation than originally planned. Adjunctive therapy was required in fewer than 20% of the patients. Concern over restenosis has been raised with atherectomy devices. Zeller et al reported technical success in 97% of lesions intervened upon; however, at 6 months, 22% of these lesions had restenosis of greater than 70%.[37] In a prospective database, which included both patients with claudication and CLI, the overall technical success rate was 87.1% in the 66 limbs that were intervened upon.[38] In the group with CLI, the 12-month primary patency rate was only 36%, and the secondary patency rate was 62%. However, the limb salvage rate at 1 year was 86.2%. These results underscore the concept that

only temporary improvement in blood flow is sufficient for wound healing. However, randomized trials are necessary to determine if the SilverHawk device leads to improved outcomes over BA. Current data suggest that BA provides at least equivalent outcomes to atherectomy, such as the cutting balloon, until randomized trials are available; use should be arguably limited to niche areas where stenting is best avoided.

Cryoplasty

Cryoplasty, available as the PolarCath System (Boston Scientific Corporation, Natick, MA), is a device that delivers nitric oxide as a pressurized liquid into an angioplasty balloon. During this process, nitrous oxide changes into gas, leading to balloon expansion (8 atm) in 2-atm increments. The process delivers cold thermal energy (-10°C) to the artery, which causes crystallization of fluid in the interstitium.[39] This process leads to apoptosis of smooth muscle cells, as well as less elastic recoil, negative remodeling, and neointimal hyperplasia. Theoretically, uniform balloon expansion occurs in which the incidence of intimal dissection and the need for adjunctive stenting is reduced.[40]

Initial studies demonstrated a procedural success rate of 94% for cryoplasty in the superficial femoral artery and popliteal arteries in patients with symptomatic peripheral arterial disease.[41] The BTK Chill Registry is a prospective multicenter trial of 108 patients (111 limbs) with CLI involving the infrapopliteal arteries. In this recently completed yet unpublished registry, technical success was obtained in 97% of cases with a dissection rate of 7%. Six-month and 1-year freedom from amputation rates were 93% and 85%, respectively. Kaplan-Meier analysis showed that survival from major amputation was 89% at 6 months and 79% at 1 year. Unfortunately, 22 patients initially treated were either lost to follow-up or had withdrawn by 1 year. Furthermore, as in other studies, patients with Rutherford category 6 symptoms had a much higher amputation rate (40%) than those with either category 4 or 5 (0% and 11.4%, respectively). Randomized controlled trials will need to be conducted to assess the utility of this therapy further in CLI.

Stem Cell Therapy

Using stem cell therapy to treat CLI is currently in US phase 2b clinical trials (Aastrom Biosciences, Inc., Ann Arbor, MI). This prospective, controlled, randomized, double-blinded, multicenter trial is expected to enroll 120 patients at up to 20 sites to evaluate efficacy and safety of the therapy. A mixture of stem and progenitor cells harvested from the bone marrow of the patient will be used to assess for regenerative potential in the peripheral vasculature. The patients will be followed after treatment for 12 months to assess safety, amputation rates, wound healing, and quality of life.

CONCLUSION

Due to the improvement in patient outcomes when amputation is avoided in CLI, limb salvage is a worthwhile endeavor. The BASIL trial has demonstrated that BA is an acceptable method of revascularization that is less costly than surgery in patients with CLI. Furthermore, endovascular therapies do not jeopardize distal target vessels if surgery is considered at a later date. In addition, patients with CLI who are not surgical bypass candidates due to severe comorbidities can often safely undergo endovascular revascularization.

At the current time, advancements in other methods of revascularization such as stenting, excimer laser, excisional atherectomy, and cryoplasty are occurring. However, these modalities lack randomized data. Until prospective randomized trials are available, as have been done with BA, stenting, and surgery, more expensive modalities should be reserved for niche lesions or BA failure. As the cumulative experience of operators increases, the already-promising results of endovascular therapy will continue to improve. ■

Jeffrey H. Freihage, MD, is an interventional cardiology fellow at Loyola University Medical Center in Maywood, Illinois. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Freihage may be reached at (708) 216-1144; jfreih@lumc.edu.

Robert S. Dieter, MD, RVT, is an interventional cardiologist at Loyola University Medical Center in Maywood, Illinois. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Dieter may be reached at (708) 216-1144; rdieter@lumc.edu.

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