Cryoplasty for the Treatment of Femoropopliteal Arterial Disease: Results of a Prospective, Multicenter Registry

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PURPOSE: Despite suboptimal results, angioplasty of femoropopliteal arterial lesions has been a mainstay of endovascular therapy for many years. The recent introduction of cryoplasty marks a potential advance in the ability to effectively treat peripheral arterial atherosclerotic stenoses. This article presents the results of a prospective, multicenter trial that evaluated the efficacy of cryoplasty for femoropopliteal disease.

MATERIALS AND METHODS: One hundred two patients with claudication and lesions of the superficial femoral and popliteal arteries of no greater than 10 cm were studied. All patients were treated with a primary strategy of stand-alone cryoplasty with use of the PolarCath cryoplasty system. The primary endpoints of the study were acute technical success and clinical patency at 9 months. Technical success was defined as the ability to achieve residual angiographic stenosis no greater than 30% and residual stenosis less than 50% by duplex ultrasound (US) imaging. Clinical patency was defined as freedom from target lesion revascularization within 9 months. Primary patency was defined by a duplex US systolic velocity ratio no greater than 2.0.

RESULTS: A total of 102 patients were enrolled at 16 centers. Of those treated, 31% had diabetes and 31% were active cigarette smokers. The majority of the lesions were confined to the superficial femoral artery (84.3%) and 14.7% presented with total occlusions. The mean vessel diameter treated was 5.5 mm, the mean stenosis diameter was 87% and the mean lesion length was 4.7 cm ± 2.6. The technical success rate was 85.3% with a mean residual stenosis after cryoplasty of 11.2% ± 11.2% (P < .05 vs baseline). Clinical patency in this group was 82.2%, as only 16 patients required target lesion revascularization during the 9-month surveillance period. Primary patency determined by duplex US was 70.1%.

CONCLUSIONS: Cryoplasty demonstrated a high degree of acute angiographic success and a low frequency of target lesion revascularization. The patency rate observed compares favorably to that previously documented with conventional angioplasty.

Abbreviations: ABI = ankle-brachial index, PSV = peak systolic velocity, SMC = smooth muscle cell, SVR = systolic velocity ratio, TASC = TransAtlantic Inter-Society Consensus

SINCE the development of percutaneous transluminal angioplasty 40 years ago, this technique has become the mainstay of endovascular therapy for intermittent claudication of the lower extremities (1). However, despite widespread practice, angioplasty continues to be limited acutely by arterial dissection and recoil and by suboptimal long-term patency rates, especially in more challenging lesions. Although some degree of acute dissection is inherent in most angioplasty procedures, a recent analysis demonstrated greater than desired dissection in a significant number of treated vessels (2). In addition, a contemporary metaanalysis of femoropopliteal angioplasty has demonstrated a 1-year patency rate of 59% among multiple lesion subsets (3). Stent implantation at the time of angioplasty has been used in an effort to improve endovascular outcomes.
Stent placement has improved the acute technical results of angioplasty by eliminating vascular recoil and resolving arterial dissection (4). Because of the aggressive neointimal proliferation, stent implantation of femoropopliteal arteries has done little to extend the durability of endovascular interventions, limiting their application to a “bailout” indication (5–8).

Endovascular cryotherapy, also known as cryoplasty, represents a new method of peripheral vascular intervention. Cryoplasty combines the dilatation force of angioplasty with the simultaneous delivery of cold thermal energy to the arterial wall. Both mechanisms are achieved by filling the catheter with nitrous oxide instead of the usual contrast material/saline solution mixture. Cryotherapy has been shown to biologically alter the behavior of arterial cellular components in a manner that results in a benign healing process (9). In particular, collagen fibers are unperturbed and therefore maintain the architectural integrity of the artery, whereas elastin fibers undergo a morphologic change that may limit vascular recoil. In addition, cryotherapy is capable of inducing apoptosis in smooth muscle cells (SMCs) and other cell lines that participate in the restenosis process (10).

Early clinical reports of cryoplasty for femoropopliteal disease have shown encouraging results (11). The purpose of this study was to evaluate the safety and efficacy of femoropopliteal cryoplasty in a prospective multicenter registry.

MATERIALS AND METHODS

Patient Group

The study was approved by the United States Food and Drug Administration. One hundred two patients with intermittent claudication caused by femoropopliteal arterial disease were enrolled in a prospective, nonrandomized, multicenter registry. Patients were eligible for the study if they had intermittent claudication (Rutherford category 2/3) of the lower extremities caused by de novo or restenotic lesions of the superficial femoral artery or popliteal artery that were amenable to endovascular intervention. Target lesions were classified as TransAtlantic Inter-Society Consensus (TASC) class A, B, or C stenoses or occlusions (12) with a percent diameter stenosis of at least 50%, lesion length no greater than 10 cm, and at least one vessel runoff to the foot. Tandem lesions were included in the study provided they were located within the maximum specified treatment length of 10 cm. Patients with recent myocardial infarction or stroke and those with serum creatinine levels greater than 2.5 mg/dL were excluded from the study. Additionally, patients with rest pain, ischemic foot ulceration, or in-stent restenotic lesions were not eligible for enrollment.

The study protocol received institutional review board approval at all enrolling centers and informed consent was obtained from all patients.

Technique

All patients who met the enrollment criteria of the study underwent a baseline clinical examination, resting ankle-brachial index (ABI) measurement, and lower-extremity arterial duplex ultrasound (US) examination. Before intervention, all patients were administered 325 mg of aspirin, clopidogrel (75 mg daily for 4 days before intervention or 300-mg preprocedural loading dose), and intravenous heparin or bivalirudin to maintain an activated clotting time greater than 200 seconds. Angiography was performed with use of conventional methods to identify the target lesion and confirm its suitability for the trial.

The intent of the study was to conduct cryoplasty as a stand-alone therapy, reserving stent placement as a bailout procedure for suboptimal results, and adjunct angioplasty at the discretion of the investigator. Cryoplasty was performed with use of standard interventional technique with a 0.035-inch angioplasty wire through a 7-F arterial sheath. When the lesion was identified, cryoplasty was performed with the PolarCath cryoplasty system (Cryovascular Systems, Los Gatos, CA). The components of the system include a cryoplasty catheter, a microprocessor-based inflation unit, and a nitrous oxide cylinder (Fig 1).

The system is based on traditional balloon angioplasty technology but has been modified to incorporate nitrous oxide as the inflation medium instead of the standard mixture of saline solution and contrast medium. On initiation of cryoplasty, pressurized liquid nitrous oxide is delivered via a hypotube to a balloon reservoir at the distal end of the catheter. As the liquid nitrous oxide enters the balloon, it undergoes a phase shift to a gaseous form, which causes expansion and a dilation force of 8 atm. This phase change causes an endothermic reaction that simultaneously creates a heat sink that reduces the temperature at the interface of the balloon and the vessel wall to ~10°C. The treatment cycle of simultaneous dilation and cooling lasts 20 seconds, and after passive warming of the catheter by body temperature and surrounding blood flow, the balloon is manually deflated and can be repositioned or removed.

After cryoplasty, patients received clopidogrel for 30 days and were encouraged to take aspirin indefinitely. Postprocedural examinations included an ABI measurement within 24 hours and a lower-extremity arterial duplex scan within 7 days of cryoplasty. At 3 and 9 months, patients returned for clinical assessment, ABI measurement, and arterial duplex US. All US images were obtained by the local site personnel in accordance with instructions by an independent duplex US core laboratory (Vascular Ultrasound Core Laboratory, Boston, MA).

Arterial Duplex Imaging Protocol

All sites considered for entry into the trial were surveyed by the core laboratory to determine the available
equipment, personnel, and site experience in performing lower-extremity arterial duplex US. When these surveys had been reviewed, sites determined to have adequate experience were then required to submit two consecutive representative duplex US examinations of the infringuinal arteries. The core laboratory subsequently recommended to the sponsor one of three actions based on review of these “qualifying” US studies: acceptance; requirement of further training; or rejection. For those centers requiring further training, representatives of the core laboratory went to the sites and provided hands-on training on their equipment. Subsequent to this training, two consecutive infrainguinal arterial duplex US examinations were submitted to the core laboratory. Review of these studies resulted in acceptance into or rejection from the trial. All images were recorded on super-VHS videotape. The core laboratory provided a study protocol for acquisition of the studies. The protocol described in detail appropriate duplex US technique, including grayscale image optimization, angle correction, sample volume size, pulse repetition frequency, and Doppler velocity measurements. All images were annotated according to the core laboratory protocol and all images were independently interpreted by the core laboratory technology staff. Interobserver variability was monitored with use of an internal standard operating procedure developed by the core laboratory.

Study Endpoints

The primary endpoints of the study were acute technical success of the cryoplasty procedure and clinical patency at 9 months. The technical success of stand-alone cryoplasty was defined as the ability to cross and dilate the target lesion with no greater than 30% residual angiographic stenosis and less than 50% residual narrowing by arterial duplex imaging (performed no more than 7 days after cryoplastic). Overall procedural success was defined in the same manner but included the results after adjunct stenting. Dissection was graded using the National Heart, Lung, and Blood Institute scale and significant dissection was defined by a grade of C or greater (13). Clinical patency was defined as freedom from target lesion revascularization within the study period.

Secondary endpoints included device-related serious adverse events and maintenance of blood flow as assessed by ABI and duplex US. Serious adverse events were defined as any clinical event that was fatal, life-threatening, or judged to be severe by the investigator; resulted in persistent or significant disability; necessitated surgical or percutaneous intervention; or required prolonged hospitalization. Blood flow assessment with ABI and duplex US data were all managed by the independent core laboratory. Peak systolic velocity (PSV) and systolic velocity ratios (SVRs) were recorded for all patients according to accepted criteria (14). Primary patency was determined with use of duplex US whereby restenosis was defined by a SVR greater than 2.0 at the target lesion measured at 9 months (15,16).

Statistical Analysis

The primary endpoints of the study were analyzed on an intent-to-treat basis. Quantitative variables were expressed with simple statistical methods for all group and subgroup patient characteristics. Differences in pre- and postinterventional ABI and angiographic percent diameter stenosis were considered significant at a level of \( P < 0.05 \) according to the paired \( t \) test. Survival from target lesion revascularization was calculated with the Kaplan-Meier estimate.

RESULTS

A total of 102 patients consented and enrolled in the study between November 2001 and December 2002 at 16 institutions (15 in the United States and one in Europe). We treated 61 men and 41 women with an average age of 71 years \( \pm 9 \). Cardiovascular risk factors included diabetes mellitus in 31%, hypertension in 87%, hyperlipidemia in 81%, and a history of tobacco use in 73%. During the course of the trial, two patients died of causes unrelated to the endovascular procedure (squamous cell lung carcinoma and multiple-organ failure with pneumonia). A total of 90 of the remaining 100 patients completed the intended clinical follow-up and their target lesion revascularization data are reported herein. The duplex imaging data represent scans received for 82 patients, of which the core laboratory determined that 77 (94%) were of adequate quality for independent interpretation.

Baseline lesion characteristics are listed in Table 1. The majority of the lesions were located in the superficial femoral artery, and the patients treated typically had one or two tibio-peroneal runoff vessels. The stenoses were complex, as evidenced by the percentage of occlusions and TASC class C lesions treated.

The acute and midterm outcomes with cryoplasty are reported in Table 2. ABIs improved from a baseline of 0.72 \( \pm 0.17 \) to 0.88 \( \pm 0.17 \) at 3 months and were well-maintained at 0.88 \( \pm 0.16 \) at 9 months (\( P < 0.05 \), 3 months and 9 months vs baseline). Subjective improvement in claudication was observed in 75% of patients at 3 months and in 89% at 9 months. Angiographic examples of TASC A, B, and C lesions and their acute outcomes after cryoplasty are depicted in Figures 2, 3, and 4, respectively.

The clinical patency rate in the 90 patients who completed follow-up was 82.2%, as only 16 patients required repeat revascularization during the study period. The duplex imaging–driven primary patency rate at 9 months was 70.1%, as imaging identified 23 patients with an SVR greater than 2.0.

The technical and procedural suc-
cess of 32 diabetic patients in the study was similar to that of nondiabetic patients (84.4% and 96.9%, respectively). At 9 months, 89% of diabetic patients noted improvement in their claudication and 80% had sustained improvement in their ABI. The primary clinical patency rate at 9 months in this subset of patients was 88.9%.

A total of 15 patients in the study presented with target vessels that were occluded. The technical success rate in this group was 67% and the procedural success rate was 100%, as five patients underwent adjunct stent implantation for suboptimal cryoablation. At 9 months, all patients in this subgroup reported improvement in claudication symptoms, and 89% had sustained improvement in their ABI. The primary clinical patency rate in patients with occlusions was 92.3%.

The investigators in the study performed stent implantation after cryoplasty in a total of only nine patients. None of these patients required revascularization during the trial, and all exhibited sustained improvement in ABI.

Throughout the study enrollment, there were no unanticipated adverse events associated with the use of the cryoplasty device. Other adverse events included seven patients who experienced minor vascular access complications and two patients who required prolonged hospitalization (for hypotension and hyperthyroidism, respectively). Five patients underwent target vessel revascularization at sites remote to the target lesion. Eleven patients had endovascular procedures performed in vessels other than the target vessel, and seven patients required coronary revascularization.

**DISCUSSION**

Endovascular treatment of femoropopliteal lesions has long been hindered by suboptimal patency rates. Conventional angioplasty in particular has been limited by high dissection rates and vascular recoil. Despite technical balloon modifications and variations in technique, there has been little progress in defeating the process of restenosis. The current study demonstrated a high degree of technical success in a broad selection of femoropopliteal lesions with use of cryoplasty. In addition, clinical patency rates with use of this new form of endovascular cryotherapy were favorable in comparison with historical angioplasty outcomes.

Angioplasty of femoropopliteal lesions traditionally has achieved technical and hemodynamic success in 50%–75% of cases (17). Significant dissection rates in contemporary studies of angioplasty have been reported to occur at a higher frequency than observed in our cohort (2). The technical success rate seen with cryoplasty in this trial was 85.3%, and significant dissection was seen in only 6.9% of patients treated. The apparent improvement in acute outcomes demonstrated with cryoplasty may in part explain the low rate of target lesion revascularization seen in this trial. Conventional angioplasty in a broad subset of lesions has been shown to have a patency rate of 59% at 1 year (3), whereas cryoplasty resulted in a 9-month clinical patency rate of 82% and a primary patency rate of 70%.

These findings are consistent with previously reported outcomes of femoropopliteal cryoplasty in which the 18-
month angiographic patency rate was found to be 83% (18).

This study used duplex US and target lesion revascularization to determine the patency of femoropopliteal arteries after cryoplasty. Duplex US has demonstrated reliable efficacy in determining significant stenosis (19–21), and as a method of objectively demonstrating binary restenosis (>50%), duplex US is highly accurate. However, in clinical practice, a SVR of 2.0 alone is often associated with few or no symptoms. As a result, criteria that incorporate maximum values of PSV have been developed (>250 cm/sec) in an effort to further refine the clinical application of duplex US in this setting (22). In the current study, only eight of the 23 patients with SVRs greater than 2.0 had a PSV greater than 250 cm/sec. Whereas some investigators have defined restenosis with SVR values greater than 2.5 and others have suggested that a SVR of at least 3.0 is potentially more accurate (15), we elected to use a more conservative measure of patency.

The limitations of conventional angioplasty in the superficial femoral artery and popliteal arteries have led to increasing use of stents in an effort to achieve better outcomes. Newer stent designs and materials continue to be evaluated. Two studies have reported clinical and primary patency rates of approximately 80% at 9–12 months with use of a nitinol coil stent design (23,24). The lesions treated in these studies were typically shorter and less complex than those reported herein. Successful treatment of more complex lesions with resultant patency rates of approximately 80% have alternatively been reported with use of stent-grafts (25,26). However, despite widespread use of stents, long-term patency rates are still in the range of 60%–70% at 1 year (27–29) and meaningful clinical trial data are lacking. The aggressive neointimal response to stent implantation is well-understood, and newer problems such as stent strut fractures (30) and inflammatory reactions to endografts (31) have been reported. In our study, cryoplasty required bailout stent implantation in only 8.8% of cases. Interestingly, none of the patients who received stents experienced restenosis, and all had sustained improvement in ABI. Albeit small in numbers, this experience raises the notion that cryoplasty may have a favorable impact in limiting the proliferative response to stents.

Several potential mechanisms of action, singularly or in concert, may have contributed to the cryoplasty results demonstrated in this study. The degree of vascular injury and dissection seen after angioplasty has been strongly linked to restenosis (32). It stands to reason that a more benign method for achieving vessel dilation would therefore be accompanied by less reactivity. By inducing a phase change (solidification) in the interstitial fluids of the artery, cryoplasty may modify the mechanical properties of the plaque and vessel wall in a manner that promotes a more homogeneous response to vessel dilation. As a result, cryoplasty may be more likely to produce smaller and more evenly distributed fissures in the plaque and vessel wall. The low rate of significant dissection seen in the trial grossly supports this concept.

Angioplasty outcomes are also affected by vascular recoil. Elastic recoil after standard angioplasty depends on the density of elastin in the target artery as well as the condition of the elastin fibers (33). Femoropopliteal arteries contain a high concentration of elastin fibers relative to other commonly treated vascular targets. Cryotherapy, by virtue of the formation and expansion of ice within the fibrous structure of the arterial wall, causes a transient deformation of elastin fibers and uncoiling of elastin layers (9,34). These acute changes reduce the elasticity of the arterial wall at the site of cryotherapy and may thereby limit vascular recoil after cryoplasty.

The long-term benefits of cryoplasty as it pertains to patency outcomes may be related to apoptosis of SMCs and positive remodeling. Neointimal hyperplasia results from the migration, signaling, and proliferation of SMCs into the subintima at the site of balloon dilation (35). The frequency of apoptosis is lower in restenotic lesions, suggesting that decreases in apoptosis contribute to neointimal formation by prolonging the lifespan of SMCs (36). Earlier research has documented that SMCs are inherently sus-

Figure 3. (a) Baseline angiogram of a TASC class B lesion in a patient with a chronic occlusion of the proximal left popliteal artery. (b) Final angiogram after stand-alone cryoplasty demonstrates a smooth-bordered acute outcome that is free of dissection.
ceptible to cold thermal energy and specifically can be induced into an apoptotic life cycle (10,37). At the operating temperature of cryoplasty ($-10^\circ C$), in vitro studies have shown that nearly half the SMC population present will undergo programmed cell death (38). By inducing apoptosis and thereby reducing the population of SMCs in the target vessel, cryotherapy may inhibit neointimal formation. In the current study, the mean PSV of patients with an SVR of at least 2.0 was found to decrease significantly at the treatment site from 3 months to 9 months, further supporting the mechanism of apoptosis and positive remodeling after cryoplasty. This reduction in stenosis severity is unusual after femoropopliteal intervention, in which setting the expected outcome is progression over time. Positive remodeling as a mechanism for preserving arterial lumen dimensions in the presence of atheroma has been well-documented (39). Arterial collagen content is significantly lower in arteries that demonstrate positive remodeling compared with those with constrictive remodeling (40). In addition, cellular apoptosis in the neointima and media is favorably correlated with positive remodeling after balloon angioplasty. As vascular SMCs produce collagen, their depletion via apoptosis leads to decreased collagen synthesis. Therefore, by inducing SMC apoptosis, cryoplasty may reduce the synthesis of new collagen and suppress negative arterial remodeling. However, because the original collagen matrix is not disrupted by cryotherapy, vessel integrity is maintained. The current study was a prospective multicenter registry that did not seek to randomize versus conventional angioplasty or stent implantation. Direct comparisons between these groups are therefore limited to historical references in the literature. Outcomes for femoropopliteal arterial interventions vary considerably based on patient and lesion characteristics, and therefore these data cannot be extrapolated to potential outcomes in lesions greater than 10 cm in length or in patients with critical limb ischemia. Nonetheless, we studied a wide variety of lesions with reasonable complexity and the results compare favorably with known outcomes of conventional angioplasty and stent implantation. By virtue of the 9-month primary endpoint, these data represent midterm results, and long-term follow-up will be necessary to properly evaluate the enduring impact of cryoplasty.

Cryoplasty represents a safe and effective method of treatment for arterial lesions in the superficial femoral and popliteal arteries. The ability to successfully treat femoropopliteal lesions with limited need for stent implantation is clinically desirable. The capacity to alter the expected biologic response to percutaneous intervention represents a potential improvement in endovascular outcomes.

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