CryoPlasty therapy of the superficial femoral and popliteal arteries: A reappraisal after 44 months' experience

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Objectives: **Long-term patency remains a significant hurdle in the minimally invasive treatment of arteriosclerosis in the superficial femoral (SFA) and popliteal arteries. CryoPlasty therapy (PolarCath, Boston Scientific Corp, Natick, Mass) is a novel approach designed to significantly reduce injury, elastic recoil, neointimal hyperplasia, and constrictive remodeling. The technique combines the dilatation forces of percutaneous transluminal angioplasty (PTA) with cold thermal energy applied to the plaque and vessel wall. We previously reported a technical success rate of 96% and a 12-month freedom from restenosis rate of 82.2%. However, a review of the original cohort supplemented by experience with a further 47 lesions has demonstrated less desirable results.**

Methods: **From December 2003 through July 2007, 92 lesions in 64 consecutive patients were treated and followed up for a median of 16 months with statistically significant follow-up at 24 months.**

Results: **The immediate technical success rate was 88%. Nine stents were immediately required after unsuccessful CryoPlasty (9.8%) five of which were as a result of a dissection. No unanticipated adverse events occurred, specifically, no thrombus, acute occlusions, distal embolizations, aneurysms, or groin complications. Vascular calcification was responsible for technical failure in six of the 11 immediately unsuccessful procedures. Freedom from restenosis for successfully treated lesions was 57% and 49% at 12 and 24 months, respectively. CryoPlasty of heavily calcified lesions, vein graft lesions, and in-stent stenosis faired poorly. Excluding these lesions from analysis would have resulted in an immediate success of 94% (81 of 86) and freedom from restenosis of 61% and 52% at 12 and 24 months, respectively. However, on an intention-to-treat basis, freedom from restenosis was 47% and 38% at 12 and 24 months, and CryoPlasty added approximately $1700 to the cost of each procedure.**

Conclusion: **Analysis of this expanded, longer-term data suggests that our earlier, smaller study provided an overly optimistic appraisal of the benefits of CryoPlasty. It is possible that a larger analysis might have identified a subset of patients or lesions that would benefit from CryoPlasty, but considering the additional cost, we no longer use this technique in our practice. (J Vasc Surg 2008;48:634-7.)**

Although minimally invasive treatment of atherosclerotic lesions in the superficial femoral (SFA) and popliteal arteries may be preferred to surgery, percutaneous transluminal angioplasty (PTA) and stenting are problematic, with 1-year restenosis rates as high as 60%.[1] Various alternatives have been advanced, including drug-eluting stents, atherectomy, laser-assisted angioplasty, endovascular grafts, and brachytherapy, but all pose problems and have cost consequences that potentially limit their use. Recent concerns about stent fractures and the clinical implications associated with them further drive the need for alternative therapeutic options.[2,3]

In an effort to achieve longer-term patency while minimizing the use of stents, a novel form of angioplasty, called CryoPlasty therapy (PolarCath Peripheral Dilatation System; Boston Scientific Corp, Natick, Mass), was introduced. CryoPlasty therapy builds on conventional PTA by applying cold thermal energy to the plaque and vessel wall.[4] Rather than saline, liquid nitrous oxide is used to inflate the balloon, cooling the surface temperature of the balloon to −10°C. The cooling is associated with three vascular effects that may contribute to improved acute and long-term outcomes by affecting processes implicated in restenosis: altered plaque response which makes plaque more vulnerable to dilation, reduced elastic recoil, and induction of apoptosis (noninflammatory cell death) in the smooth muscle cells.

We have previously published the early (12-month) patency results of our single-center experience with CryoPlasty.[5] This initial experience with 47 lesions demonstrated a technical success rate of 96%, with no dissections and a stent rate of 8.5%. Freedom from restenosis at 12 months was 82.2%. Because of these excellent results, we continued to use CryoPlasty routinely for a further 45 lesions in the superficial femoral, popliteal, and tibioperoneal trunk arteries as well as for stenoses in lower extremity vein bypass grafts and now have an experience spanning 44 months. A review of this enlarged patient cohort has demonstrated different results than those previously reported and prompts this new report.

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Table I. Indications for CryoPlasty[a] for failing femoropopliteal bypass grafts

Indication	*Cases, No.*
Valve cusp stenosis	1
Anastomotic stenosis	2
In-graft stenosis	3
Inflow stenosis	4
Outflow Stenosis	2

[a]PolarCath, Boston Scientific Corp, Natick, Mass.

Table II. Comorbid conditions and risk factors

History	*Patients, No (%)*	*Level 1, No.*	*Level 2, No.*	*Level 3, No.*
Diabetes	22 (34)	9	13	0
Hypertension	47 (73)	20	22	5
Tobacco	24 (38)	15	7	2
Cardiac disease	29 (45)	6	16	7
Carotid disease	42 (66)	23	19	0
Renal disease	5 (8)	3	0	2
Hyperlipidemia	43 (67)	12	19	12
Pulmonary disease	9 (14)	1	1	0

MATERIAL AND METHODS

Patients. From December 2003 through July 2007, 64 consecutive patients (71 procedures, 67 limbs, 92 lesions) were treated using CryoPlasty therapy. Concurrent with this study, our group also used other endovascular techniques such as atherectomy and subintimal angioplasty. However, to evaluate this new technique, we studied the procedure only in patients that we otherwise would have treated with balloon angioplasty and never used CryoPlasty in conjunction with these other techniques. Of the 92 lesions treated, 61 (67%) were in the SFA, 25 (27%) were popliteal, and six (6%) were in an autogenous nonreversed vein bypass graft.

The 64 patients (31 women and 33 men) were a mean age of 81 years (range, 55-95 years). Indications for treatment with CryoPlasty therapy were gangrene in 3, rest pain in 3, failing femoropopliteal graft in 11, skin ulceration in 7, and claudication in 49 (Table I). Five procedures were performed for restenosis after previous standard PTA. Two CryoPlasty procedures were for an in-stent stenosis. Some CryoPlasty treatments were performed for more than one indication. Comorbid conditions and risk factors, as determined by the Society for Vascular Surgery classifications,[6] are summarized in Table II.

Technique. Arterial access was achieved by using 6F or 7F sheaths placed through the contralateral groin except in one patient in whom an ipsilateral approach was used. Balloon lengths varied, depending on the length of the artery to be treated (2 to 6 cm), with the 2-cm and 4-cm balloon being used predominantly. According to the manufacturer, the CryoPlasty balloons are inflated to 8 atm of pressure. It is recommended that the treated area extend several millimeters beyond the lesion to help minimize dissections, because the effect of the cold temperature on healthy tissue has been demonstrated to have no negative effect.[7] Balloon diameter also varied, but usually was chosen to equal the size of the artery on a case-by-case basis. Overdilation was avoided, in accordance with our protocol of using a balloon diameter equal to the width of the normal artery and not overinflating, as we may do with standard balloons. This decision is predicated on the possible benefit CryoPlasty therapy may offer by not causing cell injury but rather resulting in apoptosis, a pathway that may lead to the development of less scar tissue or neointimal hyperplasia, or both.

All patients received intravenous heparin at a dose of 3000 to 5000 U. Reversal with protamine was at the discretion of the treating interventionalist. Manual compression was used to achieve groin hemostasis in all patients. All patients were prescribed aspirin (81 mg). All patients were followed up with duplex ultrasound (DUS) imaging and ankle-brachial pressure index (ABI) measurement in an InterSocietal Commission for the Accreditation of Vascular Laboratories (ICAVL) accredited vascular lab. Studies were performed ≤1 month of the procedure and then every 6 months thereafter. The treatment site was specifically recorded at the time of the original pretreatment DUS scan so that subsequent DUS studies could specifically evaluate that location.

A lesion was considered to be significant if it produced a velocity of 300 cm/s or a doubling of velocity compared with the flow velocity immediately proximal to the lesion, or both. Lesions were also graded according to the TransAtlantic InterSociety Consensus Classification (TASC) II. The location of the stenosis was recorded in centimeters from the femoral bifurcation by DUS evaluation and confirmed on arteriography using a radiopaque ruler placed between the patient's legs.

In our previous article, a restenosis was considered to have occurred when the post-CryoPlasty DUS scan identified a return to, or progression beyond, the velocity encountered immediately before the procedure. In this expanded study we refer to those criteria as defining "recurrence" and now define "restenosis" according to the more accepted definition of a velocity profile again >300 cm/s or a demonstrated doubling of velocity across the lesion, or both. All lesions that were subsequently treated for recurrence had confirmatory arteriographic confirmation. However, the indication for treatment was always based on clinical indications and not DUS, ABI, or arteriographic evidence of restenosis alone.

Statistical analysis. All patients were entered into a computerized registry (AtriumNetMD, Nashua, NH). The MedCalc 9.4.1.0 statistical software (MedCalc Software, Mariakerke, Belgium) was used to perform multivariate analysis of variables using Cox proportional hazards regression and to construct Kaplan-Meier curves.

Table III. Immediate technical failures after CryoPlasty[a]

Event	*No.*
>30% residual stenosis requiring standard balloon angioplasty	1
Unresponsive heavily calcified lesion requiring femoropopliteal bypass	1
Unresponsive heavily calcified lesion requiring stent	2
Dissection requiring stent for salvage[b]	5
Unresponsive non-calcified lesion requiring a stent	2

[a]PolarCath, Boston Scientific Corp, Natick, Mass.
[b]Three of the five were calcified lesions.

RESULTS

The mean follow-up was 16 months (range, 1 day-44 months). Statistically significant Kaplan-Meier curves are available for 24 months. After undergoing CryoPlasty therapy, 11 patients died of causes unrelated to the procedure. No patient has been lost to follow-up.

The procedure was performed on a median of 1.5 lesions per limb (range, 1-3 lesions). Mean lesion length for the 92 lesions was 3.9 cm (range, 0.5-45 cm). Most of the lesions were TASC A, except for 11 TASC B lesions and one TASC C lesion. Total occlusions were not treated in this series. On average there were two tibial runoff arteries (no runoff artery in 4 procedures, 1 artery in 30 procedures, 2 arteries in 25 procedures, and 3 arteries in 12 procedures).

The immediate technical success rate, defined as a residual stenosis of <30%, was 88% (81 of 92 lesions). Excluding the technical failures, the mean residual stenosis was 23.2%, although three lesions had a 30% residual stenosis. There were 11 immediately unsuccessful CryoPlasty procedures, and the cause of these failures is tabulated in Table III. Seven dissections occurred, of which five were stented and two were left untreated; both of the latter have remained patent. There were no acute occlusions and no adverse events such as thrombus, distal embolization, aneurysm, or local groin complications. All successfully treated patients were symptomatically improved, and no immediate surgical or endovascular interventions or amputations were required. The overall lesion stent rate was 9.8% (9 of 92 lesions).

The mean ABI was 0.73 (range, 0.31-1.03) before treatment and 0.89 (range 0.49-1.11) after treatment. At the initial follow-up, 28 of 67 limbs (42%) showed improvement of ABI. Vascular calcification causing incompressible arteries, pretreatment ABI of >0.85, and multiple areas of stenosis or occlusion limit the value of post-treatment ABI as a measure of technical success.

At 1 month after the procedure, DUS scans of all successfully dilated lesions showed marked improvement, with velocity profiles demonstrating absence of hemodynamic compromise (ie, no doubling of velocity across the lesion or velocity of <300 mL/s).

Two CryoPlasty procedures were for an in-stent stenosis, one of which restenosed in 4 months and the other in 12 months. Overall, 36 (39%) lesions have subsequently recurred. On an intention-to treat basis, Kaplan-Meier freedom from restenosis was 47% and 38% at 12 and 24 months, respectively (Fig). However, freedom from restenosis for successfully treated lesions (ie, excluding the 2 unsuccessful lesions and those that required immediate stents) was 56% and 48% at 12 and 24 months. For comparison with our previous manuscript, freedom from recurrence was 59% and 48% at 12 and 24 months. Target lesion revascularization after successful revascularization was 23% and 30% at 12 and 24 months. Multivariate analysis of variables including risk factors for atherosclerosis, lesion characteristics, and runoff vessels failed to identify any variable or group of variables that would predict restenosis.

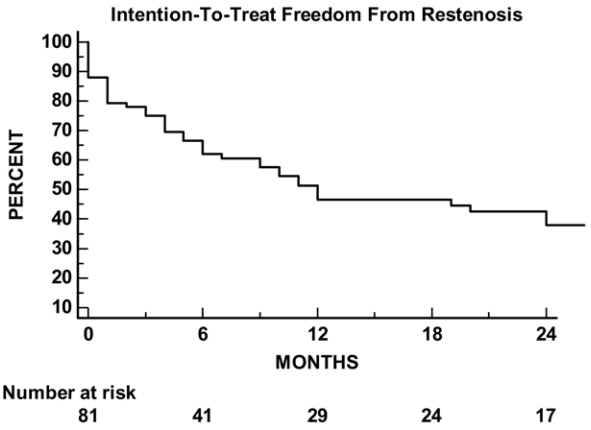

Fig. This Kaplan-Meier curve for freedom from restenosis was calculated based on intention to treat and includes all 92 procedures. The 12-month and 24-month freedom from restenosis is 47% and 38%, respectively. The curves lose statistical validity after 24 months.

DISCUSSION

Endovascular therapies for stenosis/occlusions of the superficial femoral and popliteal arteries remain disappointing, with reported 2-year patency rates of 40% to 60%.[1] Although some proponents of stents suggest improved results, many interventionalists believe that stents offer patency rates no better that a good angioplasty. Newer techniques such as laser ablation and CryoPlasty were heralded as potential improvements.[4] Our own 1-year 82.2% rate of freedom from restenosis with CryoPlasty therapy was also encouraging and suggested that this new procedure may be an advance over conventional PTA and stenting.[5] Also, a recent Cochrane review concluded that although no randomized controlled trials exist to properly evaluate this method, technical success and early primary patency results may suggest a future role for CryoPlasty in the treatment of peripheral arterial disease.[8] However, with increased experience and longer follow-up, our results appear to show no added benefit for CryoPlasty.

The immediate success rate in our series was only 88%, and freedom from restenosis for successfully dilated lesions at 12 and 24 months was only 57% and 49%. These results are very similar to those reported with standard balloon angioplasty. On the basis of intention to treat, the results of

CryoPlasty were even less compelling, with 12- and 24-month freedom from restenosis of only 47% and 38%. Freedom from target lesion revascularization rates were certainly commendable, but it must be realized that this measure of success does not necessarily imply benefit from the procedure, because many patients with restenosis were either unaware of the recurrence (it being found only by testing) or chose not to have, nor required, further therapy. Treatment for restenosis was only offered if the patients became symptomatic to a degree that they requested reintervention or bypass.

We have analyzed our expanded data to try to determine if there is an explanation for why the expanded patient experience demonstrates poorer 12-month data than originally reported. From this review it has become apparent that arterial calcification may be the Achilles heel of these procedures. If the six calcified lesions that were unresponsive or required a stent had been excluded, the immediate success rate would have been 94%, essentially the same as originally reported. Further, heavy vascular calcification as evidenced by dense opacification of the arterial wall on noncontrast arteriography was present in eight lesions that were adequately treated and three restenosed ≤6 months.

To evaluate CryoPlasty of only straightforward, noncalcified atherosclerotic lesions, we recalculated the data excluding all calcified lesions, in-stent stenosis, and vein graft lesions. The Kaplan-Meier freedom from restenosis for successfully dilated lesions would have been only modestly improved (61% and 52% at 12 and 24 months). However, multivariate analysis of variables including risk factors and lesion characteristics (including calcification) failed to define a predictor for restenosis. Further, TASC II classification also did not impact restenosis. Of the 11 TASC B and one TASC C lesions, six restenosed—but all >6 months—and seven restenosed at >2 years after CryoPlasty. We currently have no explanation for the 23% disparity in 12-month recurrence rate between the expanded and original Kaplan-Meier curves other than to suggest that the number of lesions in our original data set was too small.

Because CryoPlasty seems to offer no long-term benefit compared with standard balloon angioplasty, we have reconsidered its role in our practice. An important consideration, however, is the low dissection rate (7.6%) that we and others[5,4] have proposed may be a reason to continue using this procedure. A low dissection rate should theoretically translate into better early patency and decrease the need for costly stents. Indeed, only five stents were required for seven dissections, and three of these were in calcified lesions that we now would not consider appropriate for CryoPlasty. However, because CryoPlasty costs an average of $1700 per procedure, we believe it does not make economic sense to continue using CryoPlasty on all lesions simply to reduce the need for a few costly stents.

CONCLUSION

Evaluation of the clinical benefit of any new endovascular technique for the treatment of atherosclerotic lesions of the infrainguinal arteries needs to answer four salient questions: first, does the procedure decrease the extent of stenosis; second, is this result durable; third, does it produce clinically relevant results and: fourth, is it cost effective? Our data demonstrate that CryoPlasty can dilate most lesions, but calcified lesions respond poorly and 12% of dilations were immediately unsuccessful. The proponents of CryoPlasty would suggest that apoptosis improves durability by preventing restenosis. However, long-term patency of successfully dilated lesions was no better than reported rates for standard balloon angioplasty, with freedom from restenosis of only 57% at 12 months and 49% at 24 months. Some may infer that the low target lesion revascularization rate implies clinical relevance, but this is a poor outcome measure because it is often unrelated to the success or failure of the original CryoPlasty. Of greater clinical significance were the poor intention-to-treat rates of freedom from restenosis of 47% at 12 months and 38% at 24 months. Finally, because CryoPlasty adds approximately $1700 to the cost of the procedure, it cannot be considered cost-effective. Accordingly, we have stopped using this technology in our practice.

AUTHOR CONTRIBUTIONS

Conception and design: RS
Analysis and interpretation: RS, DP, ML, DN
Data collection: RS, KM
Writing the article: RS
Critical revision of the article: RS, DP, MP, DN
Final approval of the article: RS, DP, ML, DN, KM
Statistical analysis: RS
Obtained funding: RS
Overall responsibility: RS

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