Cryopreserved saphenous vein as a last-ditch conduit for limb salvage

Leigh Ann O'Banion, MD, Bian Wu, MD, Charles M. Eichler, MD, Linda M. Reilly, MD, Michael S. Conte, MD, *and* Jade S. Hiramoto, MD, *San Francisco, Calif*

ABSTRACT

Objective: In patients lacking autogenous vein suitable for infrainguinal bypass, cryopreserved saphenous vein (CSV) allograft (CryoLife, Inc, Kennesaw, Ga) may be an acceptable alternative. The purpose of this study was to examine outcomes of CSV conduit for infrainguinal revascularization.

Methods: Between February 2008 and August 2015, 70 patients underwent infrainguinal bypass grafts in 73 limbs using CSV. All patients lacked suitable arm or leg vein. Demographic data and patient outcomes were retrospectively collected using electronic medical records.

Results: The mean age of our cohort was 70 ± 14 years, and 36 (51%) were male; 47 (67%) were white, 39 (56%) had coronary artery disease, 27 (39%) had diabetes, 56 (80%) had hypertension, and 50 (71%) were former or current smokers. Median follow-up was 304 days (interquartile range, 130-991 days). Indications for the index operation included rest pain (27%), tissue loss (55%), and prosthetic graft infection (18%); 62 of 73 (85%) bypasses were performed for critical limb ischemia, and 45 of 73 (62%) were redo operations. Distal targets included superficial femoral artery or popliteal (38%), tibial (55%), and pedal (7%). All grafts had a minimum diameter of 3 mm. At 30 days, 55 of 64 grafts (86%) were patent; 9 were lost to early follow-up. The only significant risk factors associated with 30-day failure were ABO mismatch (43% vs 10%; $P = .05$) and donor blood type B or AB (40% vs 9%; $P = .03$). Estimated overall 1-year primary patency was 35%. In a multivariate analysis, nonblack race ($P = .05$), donor B or AB blood type ($P = .01$), and bypass to a tibial or pedal target ($P = .05$) were independently associated with loss of primary patency. There were 20 (27%) major amputations, and all grafts in these limbs had occluded at the time of amputation. Of the 33 limbs with ischemic tissue loss that had long-term follow-up, 17 of 33 (52%) went on to graft occlusion, 10 of 33 (30%) had a major amputation, and 24 of 33 (73%) had complete healing of the index wound.

Conclusions: In the setting of a multidisciplinary team with aggressive wound care, CSV may be a reasonable choice for infrainguinal revascularization in patients with ischemic tissue loss who lack autogenous conduit. However, poor midterm to long-term patency suggests that optimal selection of patients is needed to derive meaningful clinical benefit. (J Vasc Surg 2017;66:844-9.)

Single-segment autologous great saphenous vein (SS-GSV) is the ideal conduit for infrainguinal bypass grafts in patients with peripheral vascular disease.[1,2] However, in up to 25% of patients, SS-GSV is unavailable, and an alternative conduit must be used.[3] Arm veins, short saphenous veins, spliced veins, prosthetic grafts (with or without distal vein patches or cuffs), and cryopreserved saphenous veins (CSVs) have all been used for infrainguinal arterial revascularization, but none of these conduits has a patency rate comparable to that of the SS-GSV.

The presence of critical limb ischemia with concomitant infection often precludes the use of prosthetic material, leaving even fewer conduit options. CSV allograft is an attractive option in this setting, especially because of its ease of handling and "off-the-shelf" availability. Although CSV in the setting of critical limb ischemia has acceptable limb salvage rates, primary patency rates remain poor, and the high cost of the allograft may not justify its use in these situations.

Several clinical series using CSV allografts have been published, but most present short-term follow-up data.[4,5] In addition, risk factors for early and late graft failure have not been clearly elucidated. The purpose of our study was to examine clinical outcomes after infrainguinal revascularization using CSV conduit and risk factors for graft failure.

METHODS

This study was a retrospective analysis of all patients who underwent infrainguinal revascularization using

From the Division of Vascular and Endovascular Surgery, University of California, San Francisco.

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Correspondence: Jade S. Hiramoto, MD, Division of Vascular and Endovascular Surgery, 400 Parnassus Ave, A-581, San Francisco, CA 94143 (e-mail: jade.hiramoto@ucsf.edu).

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CSV allograft (CryoLife, Inc, Kennesaw, Ga) at the University of California, San Francisco between February 2008 and August 2015. As this was a quality improvement activity using coded data, review by the University of California, San Francisco Institutional Review Board was not required. Patients who underwent lower extremity bypass using autogenous vein or prosthetic conduit were excluded from the study. Demographics of the patients, comorbid conditions, medications, indications for surgery, procedural data, complications, and clinical outcomes were extracted from the electronic medical records.

Patients presenting with tissue loss were managed by a multidisciplinary limb salvage team consisting of vascular surgeons, podiatrists, and nurse practitioners. All patients had unsuitable (<2.5 mm) GSVs, short saphenous veins, and arm veins as determined by preoperative ultrasound evaluation. CSV grafts were thawed and prepared according to the manufacturer's instructions. ABO-matched grafts were preferred whenever possible on the basis of availability. All CSV grafts had a minimum diameter of 3 mm. Patients were heparinized during the procedure to a goal activated clotting time of >250 seconds. After completion of the bypass, intraoperative angiography or duplex ultrasound was performed at the discretion of the attending surgeon. Postoperative antiplatelet therapy or anticoagulation was also prescribed at the discretion of the operating surgeon. We do not use immunosuppressive therapy to augment CSV graft patency at our institution. Postoperative clinical and duplex ultrasound imaging follow-up generally occurred at 1 month, 3 months, and every 6 months. The decision to intervene on a failed or failing graft was made on an individual basis by the operating surgeon.

Primary end points were primary patency and amputation-free survival (AFS). AFS was defined as freedom from major ipsilateral amputation above the ankle or freedom from death of any cause. All analyses were performed using STATA/SE version 10.1 (StataCorp LP, College Station, Tex). Race was dichotomized to blacks vs nonblacks (white, Hispanic, Asian). Continuous variables between groups were compared with the Student *t*-test, and proportions between groups were compared with the χ^2 or Fisher exact test. Primary patency, patient survival, and AFS were estimated using Kaplan-Meier analysis. A multivariable Cox proportional hazards model was used to evaluate risk factors for primary patency. Risk factors with a *P* value of ≤ .20 in our univariate analysis were included in the multivariable model.

RESULTS

From February 2008 to August 2015, 70 patients underwent infrainguinal bypass grafts in 73 limbs using CSV. The mean age of our cohort was 72 ± 14 years, and 36 of 70 (51%) were men; 47 of 70 (67%) were white, 39 of 70 (56%) had coronary artery disease, 27 of 70 (39%) had diabetes mellitus, and 50 of 70 (71%) were former or current smokers. Preoperatively, 47 of 70 (67%) were taking a statin medication; 20 (29%) patients were receiving preoperative anticoagulation therapy, and 58 (83%) were receiving preoperative antiplatelet therapy (Table I). Indications for surgery included ischemic rest pain alone (27%), tissue loss (55%), and prosthetic graft infection (18%). In 45 limbs (62%), revascularization was performed to a tibial or pedal target, and 45 limbs (62%) had a prior failed bypass of the ipsilateral leg (Table II). ABO-crossmatched CryoVein grafts were performed in 59 of 73 (81%) limbs (Table II).

All patients who were anticoagulated preoperatively continued their anticoagulation postoperatively, with the exception of one patient who had completed treatment for a previous lower extremity deep venous thrombosis. An additional seven patients were prescribed postoperative anticoagulation (all taking warfarin) at the discretion of the attending surgeon for what was considered a high-risk graft. Postoperatively, 67 of 70 patients (96%) were receiving some form of antiplatelet therapy. Of the three patients not receiving postoperative antiplatelet therapy, two were receiving anticoagulation and one was noncompliant with medical therapy.

Median follow-up was 304 days (interquartile range, 130-991 days). At 30 days, 55 of 64 (86%) grafts were patent as determined by ultrasound or clinical examination; 9 were lost to early follow-up. The only significant risk factors associated with 30-day failure were ABO mismatch (43% failures with ABO mismatch compared with 10% without ABO mismatch; $P = .05$) and donor blood type B or AB (40% vs 9%; $P = .03$).

Estimated 1-year primary patency was 37% (Fig 1, *A*). One-year primary patency was 51% when bypass grafts were performed to the superficial femoral or popliteal artery and 24% when performed to a tibial or pedal artery (Fig 1, *B*). A univariate analysis of risk factors for loss of

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective single-center cohort study
- **Take Home Message:** In 73 limbs, most with critical ischemia, cryopreserved saphenous vein allografts resulted in only 35% 1-year patency, but 73% of the limbs with ischemic wounds had complete wound healing.
- **Recommendation:** Cryopreserved saphenous vein may be a reasonable choice for infrainguinal revascularization in patients with ischemic tissue loss who lack autogenous conduit. However, poor midterm to long-term patency suggests that optimal selection of patients is needed to derive meaningful clinical benefit.

Table I. Demographic information of the patients (N = 70)

Characteristic	Mean ± SD
Age, years	72 ± 14
Body mass index, kg/m^2	26 ± 7
	No. **%**
Male	36 51
Race/ethnicity	
White	47 67
Black	10 14
Hispanic	2 3
Asian	11 16
Comorbidities	
Coronary artery disease	39 56
Diabetes mellitus	27 39
Smokers (former or current)	50 71
Hypertension	56 80
Chronic kidney disease (GFR <60 mL/min per 1.73 m^2)	17 24
Preoperative medications	
Anticoagulation	20 29
Warfarin	17 24
Apixaban, fondaparinux, or rivaroxaban	3 4
Antiplatelet	58 83
Aspirin	36 51
Clopidogrel	8 11
Dual therapy	15 21

GFR, Glomerular filtration rate; *SD*, standard deviation.

Table II. Operative details (N = 73 Limbs)

	No.	%
Operative indication		
Ischemic rest pain alone	20	27
Tissue loss	40	55
Graft infection	13	18
ABO match	59	81
Revision operation	45	62
Conduit orientation (reversed)	73	100
Inflow artery		
Common femoral	54	74
Superficial femoral	13	18
Popliteal	6	8
Outflow artery		
Popliteal	28	38
Tibial	40	55
Pedal	5	7

primary patency demonstrated that donor B or AB blood types and bypass to a tibial or pedal target were significantly associated with loss of primary patency. Female sex and nonblack race approached but did not reach statistical significance (Table III). In a multivariable Cox proportional hazards model, nonblack race, donor B or AB blood type, and a bypass to a tibial or pedal target were significant risk factors for loss of primary patency (Table IV). Estimated 1-year secondary patency was 45% (Fig 2). Five limbs were intervened on for a failing bypass, and eight limbs were intervened on for a failed bypass.

There were 20 (27%) major amputations in this cohort, and all grafts in these limbs had occluded at the time of amputation. One-year AFS was estimated at 63% (Fig 3, *A*), and it was significantly higher in patients undergoing bypass grafts to the superficial femoral or popliteal artery (79%) compared with a tibial or pedal artery (53%; $P = .02$; Fig 3, *B*). Of the 33 limbs with ischemic tissue loss that had long-term follow up, 17 of 33 (52%) went on to graft occlusion but 24 of 33 (73%) had complete healing of the index wound. One of these patients developed a new wound on the index limb requiring major amputation, resulting in 10 of 33 (30%) major amputations in this group of patients; 9 of 20 (45%) limbs undergoing CSV bypass for rest pain required a major amputation after graft occlusion.

None of the patients in this cohort developed an infection of the cryopreserved allograft. One patient developed aneurysmal changes in the allograft but maintained graft patency. Estimated overall survival of the cohort at 2 years was 90%.

DISCUSSION

CSV has been used as a conduit for lower extremity revascularization in the absence of autologous vein.[4-7] Our study, similar to previous studies, demonstrated relatively poor 1-year primary patency rates (37%). However, we had acceptable 1-year limb salvage rates in a high-risk cohort with threatened limbs, the majority of whom had already undergone a previous failed infrainguinal bypass. In patients with ischemic ulceration, the majority (73%) were able to have complete wound healing even if the bypass graft subsequently occluded. On the basis of this experience, we believe that the use of CSV for infrainguinal revascularization may be an acceptable choice in selected patients with minor tissue loss who lack other options. In contrast, we recommend extreme caution in using CSV grafts for patients with disabling claudication or ischemic rest pain alone as clinical durability is severely limited.

Several studies have shown that there may be a component of "rejection" that occurs with the use of CSV that is mediated by both humoral and cellular responses.[8-10] We found ABO mismatch to be associated with early bypass graft occlusion, and the use of a donor vein with B or AB blood type was associated with both early and late graft occlusion. Several other studies have suggested that these factors may contribute to adverse limb-related events in the setting of CSV for

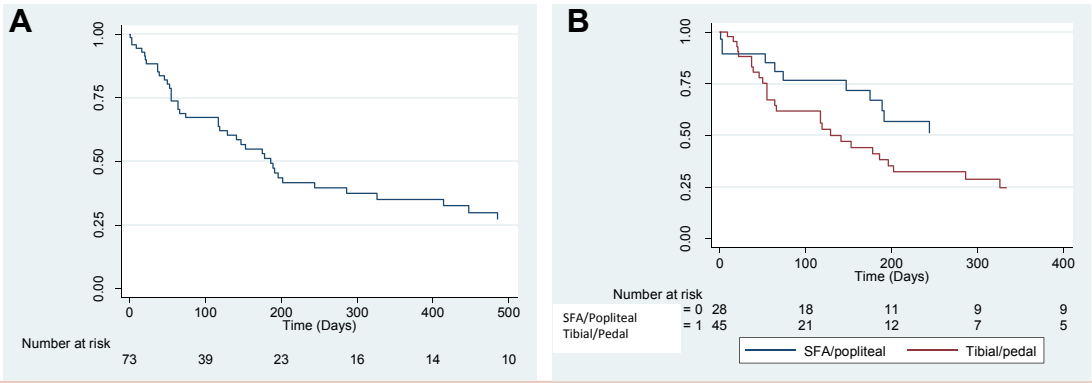

Fig 1. A, Overall 1-year primary patency. **B,** Primary patency by distal target revascularized. *SFA,* Superficial femoral artery.

Table III. Univariate analysis: risk factors for primary patency

	P value		*P* value
Age	.75	Blood type	
Female sex	.09	Non-O vs all others	.7
Nonblack race	.09	Mismatch	.48
CAD	.40	Donor B or AB	.02
DM	.59	Target artery	
Dialysis	.20	Tibial or pedal vs popliteal	.04
CKD	.81	Statin use	.64
Smoking	.86	Postoperative anticoagulation	.78
HTN	.28	Postoperative antiplatelet	.25
Hyperlipidemia	.21	Prior ipsilateral bypass graft	.55

CAD, Coronary artery disease; *CKD,* chronic kidney disease; *DM,* diabetes mellitus; *HTN,* hypertension.

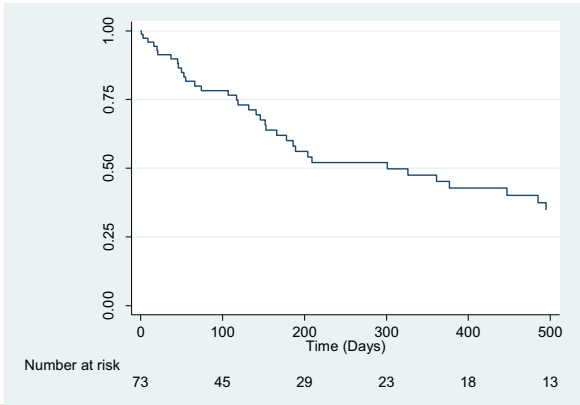

Fig 2. Overall 1-year secondary patency.

Table IV. Multivariable analysis: risk factors for primary patency

Risk factors and hazard ratios for primary patency			
		Primary patency	
Factor	No. (%)	Hazard ratio (95% confidence interval)	*P* value
Female sex	36 (49)	1.73 (0.93-3.22)	.08
Donor B or AB blood type	10 (14)	2.59 (1.22-5.48)	.01

lower extremity revascularization. In one of the earliest studies of CSV, Ochsner et al demonstrated that ABO type-matched allografts were associated with a significantly lessened immunologic rejection response. These authors also demonstrated reduced primary patency rates in a subset of patients with non-ABO-matched CSV grafts.[10,11] Zehr et al reported a nearly 50% reduction in limb salvage rates when mismatched CSV was used.[12] In addition, non-O type blood has been associated with increased thrombotic events compared with O type blood, which may be due to increased von Willebrand factor and factor VIII levels found in AB > B > A blood types.[13,14] However, there has been no strong evidence to support the routine use of immunosuppressive therapy to improve patency rates after lower extremity bypass with CSV.[8,9] Although there are no specifications regarding ABO compatibility in the manufacturer's instructions for use, our preference, supported by the available literature, is to make an effort to ABO match the donor vein to the recipient blood type. The potential lower patency with B or AB type donor CSV should be validated in other studies.

Lower extremity bypasses to an infrageniculate vessel, especially the tibial and pedal vessels, can be challenging and has been shown in numerous studies to be associated with lower patency rates compared with revascularization to more proximal targets.[1,3,15,16] Not surprisingly, we found lower patency rates when CSV grafts were used in bypasses to tibial and pedal targets. Although not statistically significant, female sex was associated with lower primary patency rates compared with men, similar to previous studies.[17,18] The diameter of the donor vein was similar in the men and women of our cohort, but it is possible that women had smaller or more

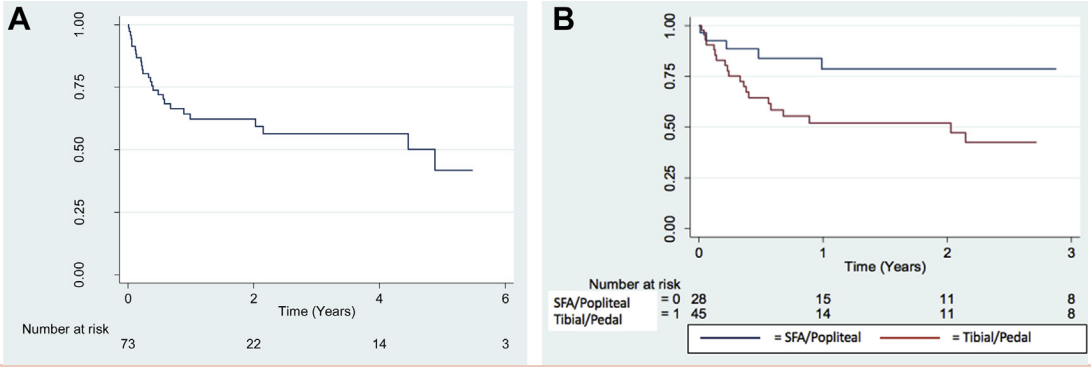

Fig 3. A, Amputation-free survival (AFS). **B,** AFS by distal target. *SFA,* Superficial femoral artery.

diseased distal target vessels compared with men. It remains to be determined whether a subgroup of patients at high risk for CSV graft occlusion may be better served with a prosthetic graft (with or without vein cuff).

We did not have a routine protocol for postoperative antiplatelet or anticoagulation therapy, although all of our patients (except one noncompliant patient) were receiving one form of therapy (or both). Although it has been postulated that anticoagulation might improve graft patency (because of the increased immunogenicity and prothrombotic nature of these conduits), most studies have found no improvement in primary patency rates with postoperative anticoagulation.[19,20] In our cohort, although anticoagulation therapy was initiated at the discretion of each individual surgeon, we did not find any difference in primary patency rates based on anticoagulation.

This study has several limitations. This was a retrospective, nonrandomized study. All preoperative workup, surgical procedures, and postoperative follow-up were performed at the discretion of the operating surgeon and not according to a strict protocol. Postoperative antiplatelet and anticoagulation management varied according to each individual surgeon. We rarely use prosthetic conduit for bypasses to a tibial or pedal target, so we do not have an appropriate comparison for this subgroup of patients. Finally, because of the retrospective nature of this study, we do not have a comparable endovascular group.

CONCLUSIONS

In the setting of a multidisciplinary team with aggressive wound care, CSV may be a reasonable choice for infrainguinal revascularization in patients with ischemic tissue loss who lack autogenous conduit. However, poor midterm to long-term patency suggests that optimal selection of patients is needed to derive meaningful clinical benefit. Prospective studies may help validate risk factors for graft occlusion and improve selection of patients.

AUTHOR CONTRIBUTIONS

Conception and design: LO, BW, CE, LR, MC, JH
Analysis and interpretation: LO, CE, LR, JH
Data collection: LO, BW, JH
Writing the article: LO, LR, MC, JH
Critical revision of the article: LO, BW, CE, LR, MC, JH
Final approval of the article: LO, BW, CE, LR, MC, JH
Statistical analysis: LO, JH
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