Cryopreserved saphenous vein allogenic homografts: An alternative conduit in lower extremity arterial reconstruction in infected fields

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Autologous saphenous veins are considered the best arterial substitute for lower extremity revascularization in infected fields. The search continues for a vascular conduit in instances when an autologous biologic grafting is not feasible. Herein we report our experience with eight patients in whom cryopreserved saphenous vein allogenic homografts were used in 10 lower extremity arterial reconstructions for limb salvage with coexisting infection. Six patients with eight prosthetic grafts including four femoropopliteal, two femorotibial, a femorofemoral, and a femoroperoneal graft required complete or partial graft excision as a result of overt infection. The two remaining patients included one with an infected femoral pseudoaneurysm and another with extensive chemical burns. All cryopreserved saphenous vein allogenic homografts were of identical match to the ABO/Rh blood groupings of the recipient patients. No immunosuppressive drugs were administered after operation. Mean follow-up was 9.5 months (range, 6.0 to 14.0 months). One patient died 5 weeks after operation with a patent graft. Two grafts occluded during follow-up; in one graft, patency was restored with thrombectomy alone. The remaining seven arterial reconstructions continue to be patent with no evidence of aneurysmal dilation with complete eradication of the primary infection. These preliminary findings suggest that cryopreserved saphenous vein allogenic homografts can serve as interim conduits for lower extremity arterial reconstruction to preserve limb viability when autogenous conduits are unsatisfactory or unavailable. Further definitive reconstruction may thereafter be necessary once sepsis is eradicated and sufficient wound healing is achieved. (J Vasc Surg 1992;15:519-26.)

One of the most formidable challenges confronting the vascular surgeon is the management of serious infections of prosthetic grafts or native artery in the infrainguinal position. General management principles include excision of the infected conduit, appropriate and intensive antibiotic therapy, wide debridement, and drainage. Even with adherence to these established principles, the risk of major limb loss or death or both is high.

Although a prosthetic conduit can be used for arterial reconstruction in the presence of an overt infection, it is imperative that it is positioned in a sterile extraanatomic plane remote from the infected field. When remote bypass is not feasible, the use of autologous tissue grafts has been proven to be durable and resistant to reinfection, and it represents the best material for direct reconstruction in an infected field. Unfortunately, autologous tissue is not always available because of multiple previous operative procedures that exhaust the supply of autogenous conduits including the greater saphenous, lesser saphenous, and arm veins. In other situations the autograft may be qualitatively or quantitatively deficient as a result of previous vein stripping, varicosity, venous anomaly, or thrombophlebitis.

Having been faced with this dilemma, we were encouraged by earlier reports describing the successful use of human venous homografts for arterial vascular reconstruction. This report describes our
Table I. Lower extremity arterial reconstructions with cryopreserved saphenous vein homografts

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Primary infection site (location)</th>
<th>Bacterial organism</th>
<th>Purulence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>Femoropopliteal PTFE; entire length of graft infected, “immersed” in purulence</td>
<td>Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, Proteus mirabilis, S. epidermidis</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>M</td>
<td>Femoropopliteal PTFE; proximal common femoral anastomoses infected</td>
<td>S. epidermidis</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>F</td>
<td>Femoropopliteal PTFE; proximal common femoral anastomoses infected</td>
<td>S. aureus</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>Femoropopliteal PTFE; entire length of graft infected, chronic tibial osteomyelitis</td>
<td>S. aureus (MRSA)</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>F</td>
<td>Femoral-anterior tibial PTFE, distal anastomoses-infected</td>
<td>S. aureus</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>M</td>
<td>Femorofemoral PTFE + Femoropopliteal PTFE; entire lengths of grafts infected, “immersed” in purulence</td>
<td>S. aureus (MRSA), Pseudomonas aeruginosa</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>73</td>
<td>M</td>
<td>Femoral pseudoaneurysm; intraaortic balloon pump segmental transmural common femoral arterial necrosis</td>
<td>S. aureus</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>Extensive lower extremity circumferential 3 inch chemical burns; nonhealing open wounds with exposed popliteal fossa; arterial insufficiency</td>
<td>S. aureus, Proteus mirabilis, Escherichia coli</td>
<td>-</td>
</tr>
</tbody>
</table>

M, Male; F, female; R, right; L, left; AT, anterior tibial; PT, posterior tibial; PTFE, polytetrafluoroethylene; MRSA, methicillin-resistant S. aureus; BKA, below-knee amputation; CVA, cerebral vascular accident; MI, myocardial infarction; A&W, alive and well.

*Composite cryopreserved homograft vein-vein conduits.
†AVS homograft reconstructions used previous proximal prosthetic graft anastomotic sites for reanastomoses; distal anastomoses varied depending on angiographic runoff.
‡Patency determined by serial color duplex examinations and ankle indexes.

Recent experience with the use of cryopreserved saphenous vein allogenic homografts to reestablish vascular continuity within an infected field. Successful eradication of the primary infection and limb salvage was accomplished in all eight patients.

PATIENTS AND METHODS
Patient population

Between July 1989 and June 1990, eight patients with overt infrainguinal graft or arterial infections underwent arterial reconstruction with cryopreserved saphenous vein allogenic homografts. Five men and three women with a mean age of 68 years (range, 61 to 80 years) underwent the procedure (Table I).

Six patients had infections involving eight previously implanted infrainguinal prosthetic grafts. Of this group, four patients had femoropopliteal polytetrafluoroethylene grafts. The two other patients had multiple grafts; one patient had bilateral femorotibial and another had a femorofemoral crossover combined with a sequential femoropopliteal reconstruction. The original graft operations were performed at another institution in six of the eight reconstructions. At the time of admission, only three of the eight infected grafts were patent. The average time between graft placement and onset of clinical infection was 23 months (range, 3 to 60 months). Four of the six patients were admitted with an inguinal wound infection associated with an exposed graft and purulent drainage. The other two patients had similar open, infected wounds at the distal anastomotic incision. After partial or entire graft removal, restoration of lower limb arterial circulation was required to avoid severe of limb ischemia.

Two additional patients had no previous prosthetic graft implantation. One patient had an infected femoral pseudoaneurysm after removal of an intraaortic balloon pump with associated surrounding soft tissue necrosis. The other patient had an extensive, full-thickness circumferential alkaline chemical burn with nonhealing infected open wounds of the lower extremity exposing the deep popliteal fossa. Both patients had significant distal lower extremity arterial insufficiency caused by preexisting arterial occlusive disease.
<table>
<thead>
<tr>
<th>Arteriogram distal runoff</th>
<th>Homograft reconstruction† (reverse configuration)</th>
<th>Conduit length (cm)</th>
<th>Duration patency‡ (mo)</th>
<th>Outcome/limb salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3: AT</td>
<td>Femoral-anterior tibial; subcutaneous tunnel</td>
<td>70</td>
<td>11</td>
<td>Patent, A&amp;W/(+)</td>
</tr>
<tr>
<td>2/3: PT peroneal</td>
<td>Femoral-distal popliteal; subcutaneous tunnel</td>
<td>53</td>
<td>10</td>
<td>Patent, A&amp;W(+)</td>
</tr>
<tr>
<td>0/3: blind popliteal</td>
<td>Femoropopliteal; (blind pop segment) subartorial tunnel</td>
<td>34</td>
<td>6</td>
<td>Patent, A&amp;W(+)</td>
</tr>
<tr>
<td>1/3: PT</td>
<td>Femoral-posterior tibial; subcutaneous tunnel</td>
<td>64</td>
<td>10.5</td>
<td>Occluded at 7 mo. 2 degrees patency after thrombectomy/(+)</td>
</tr>
<tr>
<td>R: 1/3: AT</td>
<td>(R) femoral-anterior tibial; subcutaneous tunnel</td>
<td>63*</td>
<td>7.5</td>
<td>Patent/(+)</td>
</tr>
<tr>
<td>L: 2/3: PT peroneal</td>
<td>(L) femoral-posterior tibial; subcutaneous tunnel</td>
<td>62*</td>
<td>6.5</td>
<td>Patent, A&amp;W/(+)</td>
</tr>
<tr>
<td>1/3: peroneal</td>
<td>Femorofermal; suprapubic subartorial tunnel</td>
<td>29</td>
<td>14</td>
<td>Patent/(+)</td>
</tr>
<tr>
<td>3/3: PT: AT peroneal</td>
<td>Femoral-peroneal; subartorial tunnel</td>
<td>59</td>
<td>1</td>
<td>Occluded at 1 mo./(-) (BKA) A&amp;W, s/p CVA</td>
</tr>
<tr>
<td></td>
<td>ilioprolapta femoral; in vivo reconstruction</td>
<td>18</td>
<td>5 weeks</td>
<td>Patent/(+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death at 5 weeks-MI</td>
</tr>
<tr>
<td>2/3: popliteal, PT: peroneal</td>
<td>Femoropopliteal; subartorial tunnel</td>
<td>38</td>
<td>8</td>
<td>Patent, A&amp;W/(+)</td>
</tr>
</tbody>
</table>

**Homograft procurement and preparation**

Allogenic homograft saphenous veins were procured primarily through the University of Chicago Cryogenic Laboratory (UC CryoLab), Chicago, Ill. Select organ procurement agencies and tissue banks including the Virginia Tissue Bank, Virginia Beach, Va. and Cryolife Cardiovascular, Inc., Marietta, Ga., which meet the quality requirements of the United Network for Organ Sharing and the American Association of Tissue Banks also provided cryopreserved saphenous vein homografts for implantation. All vein segments were matched to recipients by ABO/Rh blood groupings.

The saphenous veins were obtained from either donors who had no brain activity (brain dead) but who had a heartbeat and other organ procurement methods or from cadaver donors after autopsy that were chilled within 2 hours of death with less than 6 hours after cessation of circulation. Strict protocol was adhered to in the procurement of these donor saphenous veins with the objective of maintaining optimum endothelial viability. Before cryopreservation, all tissues were carefully tested and screened for viral, fungal, and bacterial communicable diseases. The venous homografts were cryopreserved in a solution containing sterile 10% fetal calf serum and 10% dimethylsulfoxide (DMSO). The tissues were frozen with liquid nitrogen at a controlled rate of 1°C per minute until they reached −40°C, and they were stored in the vapor phase of liquid nitrogen at −150°C to −175°C for an indefinite period of time until they were required for vascular transplantation. Once the specimen was placed in a deep freeze, handling was kept to a minimum to guard against cycling (warming) and tissue fracture. In cases where long distance transportation of the specimen was required for implantation, the specimens were transported in a liquid nitrogen dry shipper which maintained a temperature of −175°C for several days.

**Operative management**

Operative management in the six patients with previous prosthetic grafts (Table I, patients 1 through 6) included excision of all infected prosthetic material followed immediately by cryopreserved saphenous vein allogenic homograft vascular reconstruction within the infected field. In three of these patients, the prosthetic material was only partially excised because residual segments were well incorporated and excision may have subjected adjacent structures to injury. The graft remnants were overwoven and excluded within viable tissue in all cases. All of the homografts were positioned in reversed configuration with the proximal end-to-side anastomosis to the common femoral artery identical to the
previous proximal prosthetic anastomoses. One patient (Table I, patient 5) had composite bilateral femorotibial bypass conduits that were composed of two segments of homograft veins from different donors to provide sufficient conduit length for bypass to the distal tibial arteries. In the two other patients, an iliopofunda interposition graft (patient 7) and a femoral-to-below-knee popliteal bypass (patient 8) were performed with cryopreserved saphenous vein allograft homografts (Table I) positioned in the infected field.

In all procedures, the infected wounds were liberally irrigated with sterile normal saline. The deep fascial layers were approximated over the cryopreserved saphenous vein allograft homograft arterial anastomoses to avoid desiccation. The skin and subcutaneous tissues were left open and dressed with a topical antimicrobial, silver sulfadiazine (Silvadene Creme 1%; Marion Merrell Dow, Inc., Kansas City, Mo.), and the wounds were allowed to heal by secondary intention. Appropriate spectrum intravenous antibiotics were continued throughout the patients’ hospital courses until all subsequent cultures returned negative. Mean duration of intravenous antibiotic therapy was 4 weeks.

No immunosuppressive drugs were administered after operation in any of the patients. All patients were closely monitored after operation with serial graft surveillance by use of color duplex ultrasonography (Acuson 128; Acuson, Inc., Mountain View, Calif.) to determine graft volumetric flow velocities and patency at 1-month intervals for the first 3 months and subsequently at 3-month intervals during the first follow-up year. Resting ankle pressures and waveforms were also obtained.

RESULTS

Graft patency

Patients have been monitored for a mean of 9.5 months (range, 6 to 14 months). Of the 10 lower extremity reconstructions in septic fields, one graft occluded at 1 month (Table I, patient 6). Although the precise origin of the failure is unclear, preoperative arteriography demonstrated severe distal arterial occlusive disease with poor runoff, deeming the reconstruction procedure a “last resort” salvage situation. No alternative reconstructive modalities could be offered to this patient, resulting in an above-knee amputation. Secondary patency was established in one patient who suffered a thrombosed femoral-posterior-tibial homograft bypass at 7 months after implantation (Table I, patient 4). One death occurred (Table I, patient 7) at postoperative week 5 because of a myocardial infarction after an iliopofemoral reconstruction. The graft had been functioning well up to the time of death.
The remaining seven arterial reconstructions continue to be patent with follow-up to 14 months. In this group, all limbs were salvaged (overall 89% limb salvage rate). To date, no clinical evidence exists of homograft aneurysmal dilation and the primary infection has been completely eradicated. Follow-up duplex ultrasonography revealed no hemodynamically significant stenoses or aneurysmal degenerative changes.

**Bacteriologic and histologic findings**

The predominant microorganism was *Staphylococcus* (Table 1). *S. aureus* was recovered in seven patients, including three with methicillin resistant strains of *S. aureus* (MRSA). Two patients harbored *S. epidermidis*, and in five patients, gram-negative microorganisms were cultured including *Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus mirabilis* indicating the occasional polymicrobial nature of these infections.

Histologic examination of the preimplanted cryopreserved venous wall demonstrates it to be intact with no evidence of intimal sclerosis. The medial smooth muscle cells appear hyper-eosinophilic, and most cells have pyknotic nuclei consistent with early cellular death. (Fig. 1) After 7 months of in vivo implantation (patient 4 at thrombectomy), the same arterialized homograft vein demonstrated a densely fibrotic inner wall with a centripetal zone of trophic vessels consisting primarily of capillaries and venules. This is further encapsulated by a very sclerotic, fibrous adventitial layer with dense lymphocytes infiltrating areas of focal calcification (Fig. 2).

Histologic examination of a venous homograft specimen harvested at 5 weeks after implantation (patient 7, at postmortem examination) also demonstrates the early evolution of progressive fibrosis noted in the 7-month specimen described above. A deposit of fibrin, leukocytes, and platelets was observed on the lumen surface with a surrounding band of coagulation necrosis and leukocytes in the inner media. This is further encompassed by an outer medial, which is predominantly acellular and fibrotic (Fig. 3).

**DISCUSSION**

Vascular reconstruction within an infected field remains among the most challenging technical problems in vascular surgery. This is usually predicated by
The recommended treatment of infected prosthetic grafts is excision of part or all of the infected conduit to control sepsis and avert massive hemorrhage from suture line disruption which usually results in severe distal extremity ischemia and subsequent amputation.\textsuperscript{3,10,12,21} Use of an axillopopliteal or a transobturator bypass has been advocated in situations where there is an infected groin wound.\textsuperscript{5,7,22} Although these extraanatomic techniques are acceptable methods of revascularization, the severity of the infection and the extent of arterial occlusive process may preclude their use. In the present series, infection along the entire length of the graft was commonly encountered and evident by the presence of perigraft purulence. This is consistent with experimental findings that localized graft infections tend to propagate proximally and distally.\textsuperscript{43} Autogenous graft reconstruction was described by Moore et al.\textsuperscript{8} in an experimental canine model and clinically by Ehrenfeld et al.\textsuperscript{10} and Seeger et al.\textsuperscript{9} In these reports, infected prosthetic conduits were managed by excision and concomitant reconstruction with use of autologous grafts through the infected field. The resulting mortality and amputation rate of 9% to 13% and 6% to 9%, respectively, were better than other reported modalities of treatment of prosthetic graft infections in the femoral region by excision alone.

Although these results suggest that autogenous tissue is the best conduit for vascular reconstruction in infected fields, venous autografts are not always available. In 1983 Ochsner et al.\textsuperscript{14,15} used venous allogenic homografts as arterial substitutes in 129 reconstructions in 91 patients over a 14-year period. Seventy-five of these reconstructions involved the lower extremity with the conduit in the femoropopliteal, tibial, or peroneal artery position for limb salvage. Mean patency was 22.4 ± 4.4 months, ranging from 0 to 121 months. Several other investigators had also described the use of allogenic venous homograft as arterial conduits with varying results.\textsuperscript{23–29}

The present series is based on the principal of use of a biologic conduit in an infected field for vascular reconstruction. Since the initial report by Carrel\textsuperscript{30} demonstrating the feasibility of using vein allografts in the arterial position, several reports have been published indicating generally poor long-term patency of these vascular homografts.\textsuperscript{23–29} Nevertheless, the present series demonstrates that the cryopreserved saphenous vein allogenic homografts may be used as an arterial substitute at least on a short-term basis in an otherwise desperate situation. The initial success of these allografts may be attributed to the more uniform and meticulous cryopreservation tech-

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Fig. 3. Histologic appearance of a cryopreserved vein after 6½ months (patient 4). A, Crosssection of the vein (×75); the inner wall (I) is densely fibrotic. The outer wall (O) is also sclerotic, but small blood vessels are scattered within the fibrous tissue. A zone of blood vessels, mainly capillaries and venules (arrows) is evident between the two densely fibrotic regions. B, Higher magnification of the vessels in the intermediate vascularized region (×300); capillaries and venules are evident, but in addition there are numerous lymphocytes (small arrows) and focal calcifications (large arrows).

infection of an implanted prosthetic arterial conduit. Szilagyi et al.\textsuperscript{6} in the largest series to date, found a 1.9% incidence of prosthetic graft sepsis in 3397 cases. Others have reported a higher incidence of 5% to 6%,\textsuperscript{18–20} with the average rate being approximately 2% to 3%.\textsuperscript{21,22} The mortality rate depends on the location of the graft infection, ranging from 75% in the aortic position to 13% in distal extremity graft infections.\textsuperscript{5,9} Even in situations where prosthetic graft sepsis is not life threatening, it is limb threatening, with a high incidence of amputation. Liedeweg and Greenfield\textsuperscript{4} found a 36% amputation rate in patients with femoropopliteal grafts.
niques. Previous studies have demonstrated that the use of a penetrating cryoprotectant such as dimethylsulfoxide, preserves partial endothelial integrity and therefore increases thromborestance. L'Italian et al. had also demonstrated reduction in antigenicity and prolonged cellular viability in both venous and arterial canine homografts preserved in dimethylsulfoxide.

Histologic findings demonstrated in animal models that when a homograft was placed as an arterial substitute, an early inflammatory reaction occurs as there would be with nearly any transplanted tissue, with alteration and sloughing of the endothelial cells in the early stages. Less rapid degeneration occurs of the smooth muscle with subsequent fibrous changes. A gradual fragmentation follows with eventual disappearance of the elastic tissue. Ochsner et al. have demonstrated that the perivascular fibroblastic thickening of the endothelium coupled with an adventitial inflammatory reaction usually results in a progressive centripetal narrowing of the lumen, which may lead to subsequent graft occlusion.

In this report the histologic findings observed in the three cryopreserved saphenous vein allogeneic homografts sampled at time of implantation, 5 weeks and 7 months (Figs. 1 to 3) demonstrate a progressive fibroblastic reaction involving the intima, media, and adventitia. The early finding of hypereosinophilic smooth muscle cells associated with nuclear pyknosis is consistent with cellular death even at the time of initial implantation. These findings are similar to those reported by other investigators. The lack of a demonstrable intense inflammatory reaction would suggest that venous homografts are weakly antigenic and therefore unlikely to incite any significant systemic manifestations of rejection.

Brockbank et al. had performed a functional comparison between cryopreserved and fresh canine vein endothelium, smooth muscle and connective tissue and found no significant difference. The major obstacle to the use of fresh or cryopreserved saphenous vein allografts, appears to be the immune response of the recipient. The relationship between patency and antigenicity has been repeatedly questioned. Schwartz et al. concluded that venous homografts provide a weak antigenic stimulus for rejection in an experimental canine model, negligibly sensitizing the recipients to subsequent skin grafts. Further clinical experience demonstrated that major ABO blood grouping compatibility reduced early thrombosis of fresh homografts implanted in the arterial position. Histocompatibility matching between donor and recipient affected the rate but not the final occurrence of fresh venous homograft rejection in genetically characterized dogs. The process of cryopreservation is as yet an evolving field, and it may indeed modulate homograft antigenicity, although no conclusive evidence is available to substantiate this hypothesis at the present time. Theide et al. found that unmodified veins were normally antigenic in inbred rats, however antigenicity significantly decreased with devitalized allografts. Other investigators have also substantiated this inverse relationship between preservation of tissue viability and antigenicity. In this report all patients had functional grafts with no clinical evidence of a rejection phenomenon. This observed antigenic compatibility supports the proposition that allogeneic homografts may be suitable conduits in desperate situations when autologous grafts are unavailable.

It should be emphasized that although autogenous biologic grafts have been found to be most efficacious in the management of infected vascular reconstructions, venous or arterial homografts like autogenous grafts are still susceptible to disruption if infected by virulent organisms. The extent and virulence of the underlying infections should therefore be carefully considered when in situ biologic grafting is planned. Historically, homografts exhibit mediocore, even poor long-term patency rates. This preliminary and limited experience suggests, however, that in select instances when wound and soft tissue infection precludes the use of prosthetic grafts, most of these conduits appear to function satisfactorily and are resistant to infection when combined with aggressive antibiotic therapy. Cryopreserved saphenous vein allogeneic homografts can therefore serve as short-term, transitional or interim conduits to maintain distal limb perfusion until sepsis is controlled and wound healing achieved. The period of time that must pass before a new prosthetic graft may be placed in a previously infected field remains unclear. Definitive reconstruction may thereafter be necessary if these venous allografts occlude or degenerate.

REFERENCES


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