Venous reflux repair with cryopreserved vein valves

Peter Neglén, MD, PhD, and **Seshadri Raju, MD,** *Jackson, Miss*

Purpose: **The purpose of this study was to evaluate the immediate and short-term outcome of inserted cryopreserved vein valve allografts and the clinical outcome of treated limbs.**

Method: **Twenty-seven cryovalves were inserted in 25 postthrombotic limbs because of active leg ulcer (20 limbs) or severe disabling leg pain (five limbs) as a procedure of last resort. Previous venous surgery had been performed in 80% of the limbs. Main stem superficial reflux and iliac venous outflow obstruction were controlled before cryovalve insertion. The most common insertion site was the superficial femoral or popliteal vein. Patients were followed up with clinical examination and with intermittent duplex Doppler scanning or ascending venography to assess patency and competency of the valve station.**

Results: **After thawing, but before insertion, 74% of the cryovalves were incompetent and needed repair with transcommissural valvuloplasty. After insertion, mortality was zero. Morbidity was 48%, mainly because of seroma formation and deep wound infection. One cryovalve was explanted because of acute rejection. Six cryovalves occluded early (<6 weeks), and five occluded late. Cumulative rates of patent cryovalves and both patent and competent cryovalves at 24-month follow-up were 41% and 27%, respectively. Cumulative ulcer recurrence-free rate at 36 months was 50%. Pain relief was poor, and degree of swelling remained the same.**

Conclusion: **Compared with autologous vein transfer, cryovalve insertion is associated with high morbidity, high occlusion rate, poor cumulative midterm rate of patent graft with competent valve, and poor clinical results. The procedure should not be used as a primary technique for valve reconstruction, and it is questionable whether it is useful even in patients in whom autologous reconstruction techniques have been exhausted. The basis of the high failure rate is unclear; it may be immunologic or due to loss of endothelial cover after implantation. If cryovalves are to be a viable valve repair alternative, improved cryopreservation technique, immunologic modifications, or better matching must be achieved. (J Vasc Surg 2003;37:552-7.)**

Internal and transcommissural valvuloplasty procedures provide the best long-term patency with competent valves.[1-3] This type of repair cannot be accomplished, however, when the valve leaflets have been destroyed beyond repair, typically in patients with postthrombotic disease of the deep veins. In such cases an autologous axillary vein transfer must be performed to control deep venous reflux. Although this is the best available autologous vein transplant procedure, it is by no means an optimal alternative. Even bilateral exploration of the armpit reveals no usable valve station in 14% of patients. Although an axillary vein is present, it is found incompetent in 44% of upper limbs. Most (92%) can be repaired with transcommissural valvuloplasty in situ. Still, approximately 15% of transferred valves remain mildly leaky after insertion.[4,5] Therefore the ultimate goal in venous surgery is to find an off-the-shelf valve to replace the defunct valve in the deep venous system. The commercial availability of cryopreserved venous valve allografts (or cryovalves) has held the promise of fulfilling that goal. Initial clinical experience suggested that the cryovalve is a safe biovalve substitute with reasonable patency and competency in the short term and therefore can be inserted as a last resort salvage procedure in selected cases.[6] In clinical practice, we evaluated use of cryopreserved venous valve segments to control postthrombotic deep venous reflux in limbs with severe chronic venous insufficiency. The study was performed prospectively and on an intent-to-treat basis. Immediate and midterm clinical outcome of the treated limb and of the inserted cryovalve venous segments is described.

MATERIAL AND METHODS

Between September 1997 and December 2001 we studied 25 patients with severe postthrombotic disease (left limb = 16, right limb = 9; men = 17, women = 8; median age, 44 years, range, 32-81 years). The primary indication for valve surgery was active venous stasis ulcer in 20 patients, and severe postthrombotic pain and lipodermatosclerosis or stasis dermatitis in five. The median duration of symptoms was 7 years (range, 2-20 years). Thrombophilia testing yielded positive results in 14 of 23 tested patients (61%), including protein S or protein C deficiency in 6, anticardiolipin immunoglobulin M and immunoglobulin G positivity in 5, antithrombin III deficiency in 2, and presence of Leyden factor in 1. Cryopreserved venous valve allografts were inserted as a salvage procedure after other methods of valve reconstruction were either unavailable or had been exhausted. Last-resort treatment was indicated because 20 of 25 limbs (80%) had undergone previous venous procedures in addition to conservative treatment with compression and ulcer care (Table I). Main stem superficial reflux and iliac venous outflow obstruction, if present, were controlled before surgery, leaving the axial deep reflux as determinant.

From the River Oaks Hospital, Jackson, Mississippi.
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Reprint requests: Peter Neglén, MD, PhD, 1020 River Oaks Dr, Ste 480, Jackson, MS 39232 (e-mail: neglenmd@earthlink.net).
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Air plethysmography (APG-1000; ACI Medical Inc, Sun Valley, Calif), duplex Doppler scanning with standardized compression, and ascending and descending venography were performed, and arm-foot pressure differential, dorsal foot venous hyperemia pressure, and ambulatory dorsal foot venous pressure measurements were obtained in all patients before surgery, as described.[7-9] Results of preoperative venous function studies are given in Table II. All limbs had marked axial deep venous reflux, but in six limbs a combination of venous outflow obstruction and reflux was observed (grade 2 or higher, Raju classification[9]). Results of the Raju pressure-based test were positive, probably because of infrainguinal obstruction, because iliac venous outflow had been ensured with venous stenting when necessary (Table I). CEAP classification, according to Reporting Standards of the International Society for Cardiovascular Surgery and the Society for Vascular Surgery,[10] was $C_{6s}E_sA_dP_r$ in 14 limbs, $C_6E_sA_dP_{r/o}$, in 6, and $C_{4s}E_sA_dP_r$ in 5.

A valve site amenable to repair was chosen according to findings at ascending and descending venography and erect duplex Doppler scanning. All sites were explored with the intent to perform valvuloplasty or axillary vein transfer to control deep reflux. When autologous valve reconstruction was not possible, a decision was made to insert a cryopreserved valve. In 19 of the 25 limbs cryopreserved valve insertion was performed 1 to 7 days later through the same incision; in 6 limbs a cryovalve was immediately available and inserted at the same procedure.

Twenty-seven cryovalves were inserted in 25 limbs. Twenty-three limbs received single-segment insertions, in the common femoral vein in 1, superficial femoral vein in 14, profunda vein in 3 (all limbs had axial transformation of the profunda vein with complete obstruction of the femoral vein), and popliteal vein in 5. Two limbs received dual cryovalve insertions, one each in the superficial femoral and profunda femoris veins.

Details of the surgical procedure have been described[6]; however, some aspects of the procedure were different in our study. The cryopreserved venous valve allografts ie, cadaveric superficial femoral veins, were shipped at −70° C from Cryolife (Kennesaw, Ga). ABO blood group and Rhesus factor (Rh) compatibility between donor tissue and recipient was ensured, although Rh compatibility is not required by the manufacturer. Rh compatibility may be an issue in fertile women and in patients who may require additional future cryovalve insertions. The cryovalves were shipped with appropriate certification regarding hepatitis and human immunodeficiency virus negativity in donor sera. The allograft was thawed according to a four-step protocol, meticulously followed, immediately before use. The texture and feel of the thawed biovalve are essentially no different from that of fresh autologous tissue, except for some increased variable thickness of the thawed vein.

Sizing of the cryopreserved allograft was made during surgery. An appropriate allograft width was selected to ensure an optimal diameter match to the native vein. The length of the graft varied depending on the number of valve stations used. Sufficient length of donor vein was used to prevent interference with the valve station at insertion. Comparable length of recipient vein to donor vein was removed to allow optimal fit. End-to-end anastomosis was performed with 6-0 nonabsorbable suture. The manufacturer certifies that at least one valve in each shipped segment is competent. However, 20 of 27 cryovalves (74%) were incompetent at negative or positive strip testing after being thawed. We were able to repair all refluxive valves with the transcommissural technique[3] and render them competent before insertion. In addition, 30% of vein segments contained two or more valve stations. An attempt was made in such cases to ensure that all valves in the inserted segment were competent and functional to (presumably) further improve reflux control. No distal arteriovenous fistula was used in any limb. Five thousand units of heparin was administered intravenously during surgery, followed by immediate postoperative anticoagulation with orally administered coumadin and daily dalteparin injections subcutaneously until therapeutic international normalized ratio levels were attained. All patients were encouraged to use CircAid legging (CircAid Medical Products, Inc, San Diego, Calif) postoperatively until ulcer healing. Informed consent was obtained from patients before the operation. The study was approved by the Institutional Review Board of River Oaks Hospital, Jackson, Miss.

Table I. Previous surgery in 20 of 25 limbs with cryopreserved valve insertion

Transcommissural valvuloplasty	3
Transcommissural valvuloplasty plus long saphenous vein stripping	1
Axillary vein transfer	1
Axillary vein transfer plus iliac vein stenting	1
Axillary vein transfer plus transcommissural valvuloplasty	1
Iliac vein stenting	4
Iliac vein stenting plus stab avulsion plus Palma bypass procedure (failed)	1
Iliac vein stenting plus long saphenous vein stripping plus stab avulsions	1
Long saphenous vein stripping plus stab avulsions	3
Long saphenous vein stripping plus stab avulsions plus modified Linton procedure	1
Long and short saphenous vein stripping plus stab avulsions	1
Short saphenous vein stripping plus stab avulsions	1
Popliteal vein release	1

Outcome assessment. The repaired vein site was observed regularly postoperatively with duplex Doppler scanning or ascending venography to record patency and competency of the inserted cryopreserved valve segment. Incompetence of the vein segment was defined as duration of reflux exceeding 0.5 seconds. The limb operated on was also observed clinically. The study end point of legs with stasis ulceration was healing, ie, complete epithelialization. Any breakdown of the ulcer after healing was considered a recurrence. The degree of pain was evaluated with a visual analog scale of 0 to 10, with 10 indicating the most severe pain.[10] Swelling was assessed as grade 0, absent; grade 1, pitting, not obvious; grade 2, visible ankle edema; or grade

Table II. Preoperative and postoperative hemodyamic results in 25 limbs

	Preoperative value (n = 25)	*Postoperative value (n = 16)*	P
Ambulatory venous pressure drop (%)	43 (15-87)	52 (40-80)	NS
Venous filling time (s)	6 (2-33)	8 (2-64)	NS
Venous filling index at 90% (mL/s)	4.0 (0.6-14.0)	3.8 (0.4-6.2)	NS
Ejection fraction (%)	51 (23-100)	45 (19-86)	NS

Data represent median, with range in parentheses.
NS, no significance.

3, massive, encompassing the entire leg. Venous function studies were repeated at follow-up.

Statistical analysis was performed with GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, Calif). Wilcoxon rank paired nonparametric tests were used in the appropriate setting to evaluate statistical significance. $P < .05$ was considered significant. Cumulative ulcer recurrence-free, valve competency, and patency rates were calculated by using survival analysis with the Kaplan-Meier method.

RESULTS

Mortality was zero. Wound complications occurred in 12 of 25 limbs (48%). Two limbs with superficial wound infection and one limb with cellulitis required only antibiotic treatment. In addition, 4 deep wound infections, 3 large seromas, and 1 wound hematoma required surgical drainage. Explantation of the cryopreserved vein segment was necessary in one patient 6 days after insertion, because of acute rejection clinically, later verified by immune reaction at histopathologic analysis. The removed cryovalve segment was replaced with another. Because of hematoma formation, this cryovalve was explored 2 days later. The graft was thick-walled, stiff, and incompetent, but was left in place for outflow because of a remaining lumen. The patient was lost to follow-up.

Patency and competence were detected with duplex ultrasound scanning or ascending venography in 21 of 25 limbs (23 of 27 implantation sites) at a median follow-up of 11 months (range, 1-41 months) after surgery. Forty-one percent of the implants occluded (11 of 27 sites). Six occlusions occurred early postoperatively (<6 weeks) in five patients despite adequate anticoagulation therapy. In one patient anticoagulation appears to have been inadequate after warfarin sodium treatment was being managed by the local physician. Five vein segments in four patients occluded later (3 to 17 months), apparently related to independent discontinuation of warfarin sodium by three patients and poor regulation of anticoagulation in one. Three of these cryovalves appeared competent on preocclusion ultrasound scans. Catheter-directed thrombolysis was attempted in three early occlusions but was unsuccessful. Typically, early thrombosis produced not only marked local inflammatory reaction at the insertion site but also systemic symptoms with fever and malaise. At last follow-up 12 valve sites were patent, with eight competent valves, three incompetent valves (duration of reflux, 2.5-3.7 s), and one leaky valve (duration of reflux, 0.8 s). At 24-month follow-up, cumulative rate for patent cryovalves was 41% and for both patent and competent cryovalves, 27% (Figs 1 and 2). The overall rate for patent and competent cryovalves before late occlusion in valves with and without transcommissural repair before insertion was 56% and 42%, respectively (difference not significant).

Three limbs (2 of 20 with leg ulcer and 1 of 5 with painful limb) were lost to clinical follow-up (median, 20 months; range, 2-49 months). The cumulative ulcer recurrence-free rate for 18 limbs is shown in Figure 3. At 36-month follow-up, 50% of limbs were ulcer-free. Early occlusion of the cryovalve in two limbs with ulcer resulted in healing in one and no improvement in the other. None of the patients whose main symptom was leg pain, without leg ulcer, had any improvement, explained by early occlusion of the cryovalve in 3 of 4 such limbs. There was no significant difference in median pain score for the entire group of 22 symptomatic limbs with preintervention values of 3 (range, 0-9) to 1 (range, 0-8) (difference not significant) after intervention, and the degree of swelling remained the same (median, 1; range, 0-3).

There appeared to be some relationship between ulcer healing and long-term patency and competency of the inserted cryovalve. In most limbs with ulceration (14 of 15 [93%]) there was healing of the ulcer when the cryovalve remained patent and competent 6 weeks after insertion. One patient had a massive circumferential leg ulcer, which decreased in size but never healed completely. The stasis ulcer remained healed during the observation period in all limbs with a competent and patent cryovalve (6 limbs). The ulcer recurred, however, in all limbs, and later reflux developed in five limbs in which the valve had been competent, but remained healed in three patients with late complete occlusion without reflux.

Hemodynamic tests, including ambulatory venous pressure drop, venous filling time, venous filling index at 90%, and ejection fraction, were repeated in 16 limbs after surgery (Table II). No significant change in these parameters was observed in the total group of limbs or when fractionated into groups of patent limbs, occluded limbs, and both patent and competent limbs. Thus results of these functional tests demonstrated no hemodynamic improvement.

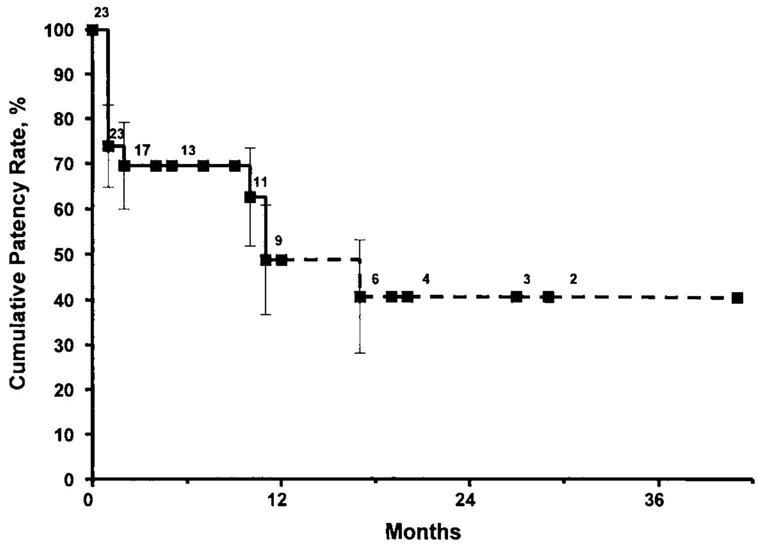

Fig 1. Cumulative patency rate of cryovalve segments. Number of limbs at risk at each interval is given, as well as standard error of the mean (± 9%-13%). *Dashed line*, SE > 10%.

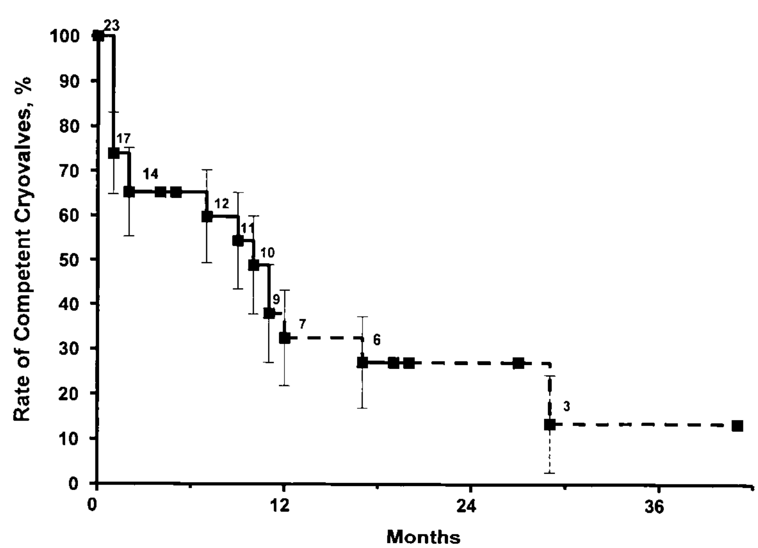

Fig 2. Cumulative rate of competent cryovalve segments. Number of limbs at risk at each interval is given, as well as standard error of the mean (± 9%-11%). *Dashed line*, SE > 10%.

DISCUSSION

Cryovalve cumulative patency and competency rates of 78% and 67%, respectively, at 6 months, described in a phase I study,[6] were similar to our study, but were not maintained with longer follow-up. At 2 years, patency and competency rates had progressively deteriorated to 41% and 27%, respectively. Autologous axillary vein transfers in a similar group of patients fared considerably better, with a lower occlusion rate (0%-18%) and higher competency rate (40% or better) than that of cryovalves at 2 years.[1,5,11,12] This study includes patients with known thrombophilia, infrainguinal outflow obstruction, and sometimes noncompliance with anticoagulation therapy. Since this graft will be used in patients with these types of disorders, the study group reflects clinical reality. In these patients, competency and patency after insertion of cryopreserved vein valve allografts are much inferior to that after transfer of autologous vein grafts.

Thrombosis may recur in the allograft as a phenomenon of the original thrombotic disease because of poor inflow and as a secondary event to graft rejection. The cause is probably multifactorial. It is obvious, however, that

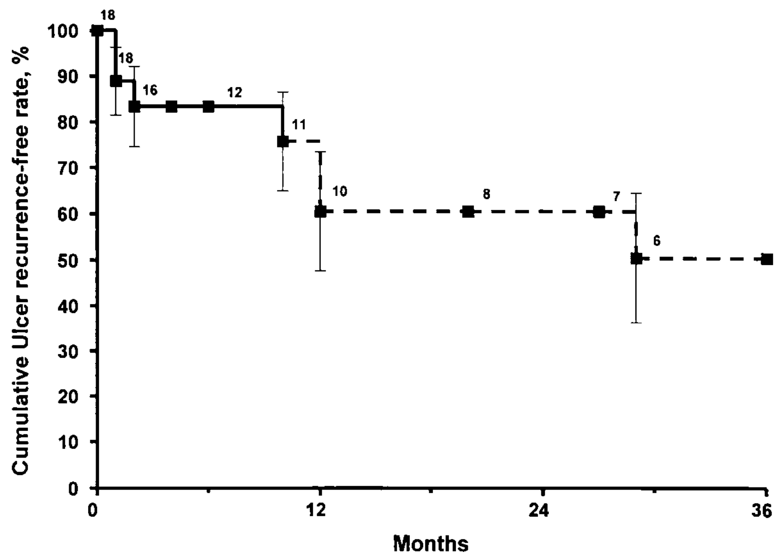

Fig 3. Cumulative ulcer recurrence-free rate for 18 ulcerated limbs after cryovalve insertion. Number of limbs at risk at each interval is given, as well as standard error of the mean (± 7%-14%). *Dashed line*, SE > 10%).

mismanagement of anticoagulation therapy contributes to occlusion of the graft. It is vitally important that anticoagulation therapy be meticulously monitored after cryovalve insertion and international normalized ratio kept at adequate therapeutic levels. When warfarin sodium is discontinued or anticoagulation is insufficient, the inserted cryovalve segment inevitably becomes occluded. This is contrary to the autologous axillary vein transfer, which has high patency with low-dose warfarin sodium treatment (1 to 2.5 mg/d with no monitoring), even in patients with severely scarred, trabeculated postthrombotic veins.[3,5] Cryovalve insertion requires more intense anticoagulation therapy to keep the valve patent than other valve repairs do. The thrombus appears to involve only the cryovalve segment, and although a marked inflammatory reaction is often observed, no further distal extension or pulmonary embolism has been noted. Occlusion can be expected even with adequate anticoagulation therapy, but the occlusion rate is lower.

The high rate of incompetence of cryopreserved venous valves after thawing is cause for concern. Three fourths of the cryovalves required a transcommissural valve repair before insertion. Competency certification by the manufacturer is based on testing of the valve with 120 mm Hg of counterflow pressure immediately before cryopreservation. Rather than faulty testing, the high percentage of reflux after thawing indicates that structural changes related to the cryopreservation and thawing procedures may occur. Thermal fractures, 50% decrease of smooth muscle and connective tissue function, and marginal decrease of venous compliance have been described.[13,14] Repaired valves did not fare any worse than nonrepaired valves.

The cumulative ulcer recurrence-free rate at 3 years was 50% after cryovalve insertion. A higher rate of 73% to 84% has been observed with autologous vein grafts in groups of similar patients.[1,2,5] As in autologous vein grafts, nonhealing or recurrence of stasis ulcer is rare when the cryovalve is competent. Thus the higher ulcer recurrence rate appears to be related to progressive failure of the repair with the cryopreserved valve. In patients in whom the graft occluded, symptoms did not always worsen. Three of five patients with initially healed ulcer had no immediate recurrence of ulcer at the time of obstruction, although this may occur later after recanalization. Total occlusion, at least in the short term, will abolish reflux and mimic a competent valve hemodynamically. The improved clinical situation was not reflected in better hemodynamic test results.

The high morbidity associated with this procedure is of concern and was thought to be linked to the immunologic reaction. One cryovalve had to be explanted because of a violent inflammatory reaction and acute rejection. Another investigator has also had this experience in one patient (Robert L. Kistner, personal communication, 2001). The cryopreserved saphenous allografts are immunogenic and elicit a response, albeit weak.[15,16] It is possible that the high morbidity is linked to an immunologic response and that ABO matching is not sufficient in these patients.

Two working theories can be suggested for why cryovalves yield results so inferior to those with autologous vein repair. One theory is based on structural damage due to cryopreservation and the other on an immunologic response. Even though the endothelium of the thawed cryovalve looks normal, we do not know whether it actually survives after insertion.[17,18] If there is damage or necrosis of the endothelium after implantation, the cause may be preservation-related or secondary to an immunologic reaction. Scanning electron microscopy of the thawed vein demonstrates apparently viable endothelium.[12,18,19] The long-term biologic viability of the endothelium after clinical insertion, however, remains uncertain.

Venous allografts are antigenic.[15,16] Cryopreservation does not seem to substantiallly diminish antigenicity. Endothelium is rich in class II antigens, whereas collagen probably expresses only minor antigens.[20] Some patients may have increased levels of preformed antibodies as a result of previous blood transfusions or pregnancy. The antigenic response may be amplified by endothelial injury from any cause. Mitigation of the immune response may lead to adaptation and preservation of the allograft matrix and allow creeping replacement of allograft endothelium with endothelium of host origin. Attempts at immunologic modulation with low-dose azathioprine in human beings has yielded poor results.[21] Newer immunosuppressive agents that act much earlier in the immune cycle, eg, cyclosporine A, may be more promising than azathioprine.[22] Early observations on insertion of decellularized cryovalve implants have also shown substantial decrease in antigenicity, which appears to enable re-endothelialization from the host.[23]

In conclusion, compared with autologous vein transfer, valve reconstruction with cryopreserved venous valve allografts is associated with high morbidity, high occlusion rate, poor cumulative midterm rate of patent grafts with competent valves, and poor clinical results. The procedure should not be used as a primary technique for valve reconstruction, and it is questionable whether it is useful even in patients in whom autologous reconstruction techniques have been exhausted. Although patients do not fare worse in the short term, and sometimes even improve, when an occlusion occurs ligation of the superficial femoral vein is a less expensive treatment.[24] The basis of the high failure rate of cryovalves is unclear. It may be immunologic or due to loss of endothelial cover after implantation. Further improvement of cryopreservation technique, immunologic modifications, and better matching must be explored if cryovalves are to be a viable alternative in valve repair.

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