Experimental studies on glycerol preserved vascular allografts

Fahner, P.J.

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Comparison of preserved vascular allografts using glycerol and University of Wisconsin solution in a goat carotid artery transplantation model

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P.J. Fahner¹, D.A. Legemate¹, A.C. van der Wal², J. van Marle³, S.L.M. Peters⁴, C.F. van Eck¹, T.M. van Gulik¹, M.M. Idu¹

¹Department of Surgery and ²Department of Pathology
Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
² Department of Pathology, AMC
³ Department of Microscopic Research, AMC
⁴ Department of Pharmacology & Pharmacotherapy, AMC
Abstract

Background. Prosthetic grafts have poor patency rates in peripheral arterial reconstructions. Glycerol (GL)-preserved grafts are an alternative. The aim of this study was to examine patency, graft morphology and function of GL-preserved allografts in a goat carotid artery animal model.

Methods. The first group (n=7) underwent bilateral replacement of the carotid artery by a carotid allograft that was preserved in GL for 1 week. In the second group (n=5), a carotid artery allograft that was preserved in University of Wisconsin solution (UW) for 48 h was used. In the third group (n=5), the jugular vein (autologous vein, AU) was used. The follow-up was 3 months.

Results. One UW graft and 1 GL graft occluded in the first 24 h postoperatively. Three-month primary patency rates for GL, UW and AU grafts were 93%, 100% and 80% respectively (p = 0.39). Graft diameter was increased in UW allografts (p < 0.005), whereas GL allografts remained unchanged. After explantation, GL allografts demonstrated contraction and relaxation capacity and lower intimal thickness (p < 0.001).

Conclusion. GL preservation has proven to be a feasible method for arterial allograft transplantation in a large animal model with decreased intimal hyperplasia and renewed functional capacity.
Introduction

Prosthetic vascular grafts have proven less successful when used as small caliber grafts (< 6mm) in peripheral arterial reconstructions compared to great diameters in aortic repair. Therefore research in small-diameter, biological or tissue-engineered vascular constructs has continued. To minimize the immunological response to allogeneic vascular grafts, current research has focused on the use of decellularized tissue matrices which are potentially repopulated by host derived endothelial and smooth muscle cells after implantation (1-4). Biological tissues provide an extracellular matrix scaffold for migrating host cells using host specific adhesion receptors. This results in diminished or absent immunological response to the grafts and enhanced ingrowth of host endothelial and smooth muscle cells (5).

The use of biological vascular grafts requires appropriate techniques for graft preservation and storage. Various preservation methods for vascular allografts have been examined in the past two decades, of which cryopreservation, glutaraldehyde tanning and cold storage have found clinical application. Early thrombosis, intimal hyperplasia and aneurysmal degeneration, however, have hampered optimal performance. Glycerol (GL) preservation of skin allografts is successfully in the management of burn injuries (6-9). Glycerol, a non-toxic intermediate of the fatty acids metabolism, leaves the structural integrity of the skin unaffected and after application on wounds, generates an unspecific host inflammatory reaction rather than an immune response leading to rejection (10;11). An additional advantage of the use of glycerol is its potency to eliminate micro-organisms (12). In vitro experiments using infected cadaveric split skin grafts showed inactivation of herpes simplex virus, polio virus, HIV-1 and elimination of bacterial growth after prolonged storage (13-15).

The efficacy of glycerol for preservation of skin allografts has encouraged examination of glycerol for preservation of vascular allografts. Previous in vitro experiments in our laboratory on glycerol preservation of rat aortic allografts confirmed maintenance of mechanical integrity and extracellular matrix characteristics after three months preservation (16). In an in vivo rat aortic transplantation model, glycerol preserved allografts showed a three months patency rate comparable to autografts, with decreased intima hyperplasia and adventitial inflammatory reaction (17).

The primary aim of the current study was to assess the use of glycerol preserved arterial allografts in a preclinical, large animal model, with special emphasis on patency rate, vessel wall function and graft morphology after implantation. Our secondary aim was to compare glycerolization of vascular allografts with cold storage preservation using the University of Wisconsin (UW), as widely used in most types of solid organ transplantation (18).

Because UW preservation is applicable for relatively short preservation times in contrast to glycerol preservation we hypothesized that glycerol preservation was a feasible preservation solution in a goat carotid artery transplantation model.
method for vascular allografts with patency rates comparable to UW preserved allografts and venous autografts.

Materials and methods

Animals and experimental groups
Dutch female milk goats (65kg - 104kg) were used, obtained from an official breeder. The animals were housed five days prior to the experiments and maintained on a 12-hour light-dark cycle. The animals had free access to water, bix and hay. The experimental protocol was approved by the Animal Ethics Committee of the Academic Medical Center, University of Amsterdam, The Netherlands. This protocol was in accordance with EU regulation on the care and use of laboratory animals. In addition, the investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 84-23, revised 1996).

The study consisted of three experimental groups. One group (n = 7) underwent bilateral replacement of the common carotid artery by a glycerol preserved carotid allograft (glycerol group, GL). In the second group (n = 5) carotid allografts cold preserved in UW solution, were used for bilateral replacement of the common carotid artery (University of Wisconsin group, UW). In animals of the third group (n = 5) unilateral autotransplantation of the jugular vein to the carotid artery was performed (autologous vein group, AU). This group served as golden standard since autologous venous allografts reached highest patency rates in peripheral arterial bypass surgery. At the beginning of the study one animal was sacrificed to serve as allograft donor. In subsequent experiments, the segments of carotid artery which were excised in order to be replaced by preserved allografts, were preserved and stored until implantation in the following animal. All grafts were harvested after 3 months follow-up.

Surgical protocol and graft preservation
The animals were premedicated with 20 mg/kg Ketamine and 0.5 mg/kg Midazolam i.m. and were ventilated using a mixture of O₂ / N₂O, 1:1 L and Isoflurane 1-1.5% after endotracheal intubation and placement of a nasogastric tube. Postoperatively, buprenorfine 5.0 µg/ kg and finadyne 1.0 mg/kg was administered i.m. for control of pain. Finadyne 1.0 mg/kg injection was repeated on a weekly basis. Ampicilline (1 g) was given 24 hours preoperatively and on day 1 and 3 postoperatively. All operations were performed under sterile conditions. Using a midline neck incision, the carotid artery and jugular vein were identified and dissected over a length of 10 cm. Three minutes before clamping of the carotid artery, heparin (100 IU/ kg) was infused.
intravenously. A vascular allograft or autograft of 6.0 cm length was implanted as interposition graft with end-to-end anastomosis using a 6.0 Prolene running suture.

The preservation protocol for the glycerol allografts was in accordance with the protocol routinely used at the Euro Skin Bank (Beverwijk, The Netherlands) and was optimized for preservation of arterial allografts (16). Briefly, the grafts were incubated in glycerol solution (Glycerolum, Genfarma BV, Maarssen, The Netherlands) of increasing concentration as follows:
1. Incubation in a glycerol 50% solution for 4 hr at room temperature
2. Incubation in a glycerol 70% solution for 3 hr at 33°C
3. Incubation in a glycerol 85% solution for 3 hr at 33°C

After completion of the protocol, the grafts were stored in glycerol 85% for one week at 4°C.

Cold storage was performed using University of Wisconsin preservation solution (ViaSpan®, Barr Laboratories, Inc., NY) in which the grafts were immersed for 48 hr at 4°C. Before implantation all grafts were rinsed in saline for 20 min.

**Graft surveillance**
Routine color duplex scanning (Hewlett Packard Sonos 5000) of the grafts was performed at post-operative day 1, 3, 7 and week 2, 3, 4, 8 and 12. Peak systolic velocity (PSV), end diastolic velocity (EDV) and vessel diameter were measured. Significant stenosis was arbitrarily defined as a PSV max which was 2.5 times increased. Just before explantation, a digital subtraction angiography (DSA) was performed by puncture of the femoral artery and placement of a 5 Fr angiographic catheter (Imager II™, Boston Scientific Corporation, Watertown) in the aortic arch. A PTFE coated steerable guide wire (2.7 Fr, Back-up Meier, Boston Scientific Corporation, Natick, USA) was manipulated into the proximal carotid artery. Five ml of radio contrast solution (Visipaque™ 320mg I/ml, Amersham Cygne BV, Eindhoven, The Netherlands) was manually injected.

**Contraction and relaxation experiments**
Segments of glycerol allografts (n=10) were tested for functional responses immediately following explantation. In these experiments, the nonpreserved carotid artery proximal and distal to the graft (n=12) served as fresh controls. After explantation, contraction and relaxation responses were studied in 4 mm segments in an organ bath set-up as described previously (16). The initial resting tension was set at 20 mN and was adjusted throughout the experiment. After one hour of equilibration, the segments were exposed three times to a 50 mM depolarizing potassium chloride solution for 5- 10 min intervals. After a rinsing procedure a concentration-response curve was constructed for L-phenylephrine (1.10⁻⁸ – 1.10⁻⁴ M) to study receptor-dependent contractile responses.
To examine endothelium-dependent relaxation of the smooth muscle cells, a concentration-response curve was constructed for methacholine (1.10^{-7} – 1.10^{-4} M) after rinsing with Tyrode’s solution and precontraction with L-phenylephrine (1.10^{-5} M). Subsequently, the segments were exposed to the NO-donor sodium nitroprusside (1.10^{-5} – 1.10^{-4} M) to determine endothelium-independent relaxation.

**Histological and electronmicroscopical examination**

**Histology**
Five-mm ring samples were used for histological examination. Of each graft two samples were examined in the proximal, mid and distal part of the graft, respectively. Sections of the native vessel proximal to the implanted graft served as controls. Immediately after harvesting, the segments were rinsed in saline, fixed in 10% formaldehyde solution (Mallinckrodt Baker, Deventer, The Netherlands), dehydrated and embedded in paraffin. Transverse sections (5µm) were stained with hematoxylin-eosin (HE) and Elastin van Gieson (EvG) and were mounted on slides for microscopic evaluation. Of each slide three measurements of intima and media were performed at 3, 6, 9 and 12 hour on a clockwise grid. A Leica LB 30 S light microscope (Leica, Wetzlar, Germany) was used in combination with the Qwin Image pro analysis software (version 2.6, Leica Imaging Systems Ltd., Cambridge).

**Scanning electron microscopy**
Luminal coverage of the graft with endothelial cells was examined using scanning electron microscopy. Ring segments were rinsed in saline and fixed for 24 hours in McDowell fixative (4% paraformaldehyde and 1% glutaraldehyde in 0.1M phosphate buffer). The samples were dehydrated in graded ethanol’s, immersed in 1,1,1,3,3,3 hexamethyl disilazan (Merck-Schuchardt) and dried at room temperature for 12 hours. Finally, the tissue segments were mounted on stubs with conductive carbon cement, sputter-coated with 20 nm gold-palladium and scanned with an electron microscope (Philips SEM 525 equipped with an Orion frame grabber) operated at 10 kV and a spot size of 50 nm.

Angiographies, functional and morphological examinations were evaluated by blinded investigators.
Statistical analysis
One way analysis of variance analysis was performed when means of three or more groups were compared. If only means of two groups were analyzed the t-test was used. To test if time of follow-up and graft location had effects on $PSV_{\text{max}}$ values, a two way ANOVA analysis was used. The log-rank test was used to compare patency rates. All statistical analysis was performed using the GraphPad Prism 4.0 program (GraphPad Software, San Diego).

RESULTS

Animal follow-up and graft patency
Thirteen out of seventeen animals underwent surgery without any complication. Two animals developed a graft occlusion within the first 24 hours postoperatively. Both suffered from postoperative complications. One in the autologous vein autograft group had a postoperative hemorrhage and thrombosis at the anastomosis requiring thrombectomy and reanastomosis. The other animal with occlusion of a glycerol allograft developed a postoperative cardiac arrest, was resuscitated and survived. No graft occlusions were observed after postoperative day one. Two animals of the UW allograft group were euthanized on postoperative day 14 and 16 respectively, due to severe respiratory distress. The grafts were harvested and autopsy revealed bilateral pneumonia with abscess formation in both animals. The 90-days primary patency rate for UW, glycerol and autologous vein grafts was 100%, 93% and 80% respectively ($p = 0.39$).

Peak systolic velocity and graft diameter
When all measurements at the different locations in the grafts were pooled, the maximal mean peak systolic velocity ($PSV_{\text{max}}$) could be depicted for all time-points during follow-up (Fig 1). No significant stenosis, was detected in any of the experimental groups. As expected, the mean $PSV_{\text{max}}$ pooled for all time-points at follow-up was lowest in the midgraft segments for all the three groups (Fig 2). Both graft location and time of follow-up did affect $PSV_{\text{max}}$ ($p = 0.03$ and $p < 0.001$). Flow velocity was significantly lower in the midgraft segments of the autologous vein grafts whereas flow velocity was higher at the proximal anastomosis of the venous allografts ($p < 0.001$). No differences in flow velocity were found between the UW and glycerol allografts.

Results of pooled diameter measurements of each graft during follow-up are shown in figure 3. The diameter of autologous vein grafts placed as interposition graft in the carotid artery was increased compared to native, non-operated jugular vein. A significant increase in diameter was shown during follow-up ($p < 0.005$) only for the UW preserved allografts. The diameter of glycerol allografts remained unchanged during 3 months follow-up.
Figure 1. Maximal mean peak systolic velocity (PSVmax) in cm/sec for carotid artery allografts preserved in University of Wisconsin solution (UW, n = 10), in glycerol (GL, n = 14) and jugular vein autografts (AU, n = 5). 1d = 1 day, 1w = 1 week, 1m = 1 month.

Figure 2. Mean peak systolic velocity (PSVmax) in cm/sec for jugular vein autografts (AU vein, n = 5), carotid artery allografts preserved in University of Wisconsin solution (UW, n = 10) and glycerol preserved allografts (GLyc, n = 14). Error bars depict SEM. pv = proximal native vessel, pa = proximal anastomosis, mg = mid graft, da = distal anastomosis, dv = distal native vessel.
Angiography
Angiography performed after three months follow-up showed a midgraft stenosis of approximately 50% in one glycerol allograft. In none of the other glycerol or UW allografts a stenosis could be detected. The diameter of the venous allografts was 2.3 times the diameter of the native carotid artery. No aneurysmatic dilatation could be demonstrated in any of the preserved allografts.

![Graph showing mean diameter (cm) of jugular vein autografts (AU vein, n = 5), carotid artery allografts preserved in University of Wisconsin solution (UW, n = 10) and glycerol preserved allografts (GLYC, n = 14) during follow-up. Error bars depict SEM. 1d = 1 day, 1w = 1 week, 1m = 1 month.]

**Figure 3.** Mean diameter (cm) of jugular vein autografts (AU vein, n = 5), carotid artery allografts preserved in University of Wisconsin solution (UW, n = 10) and glycerol preserved allografts (GLYC, n = 14) during follow-up. Error bars depict SEM. 1d = 1 day, 1w = 1 week, 1m = 1 month.

Contraction and relaxation response
All grafts showed a modest contractile response to KCL and after stimulation with KCL and phenylephrine. A dilatory response was measured after administration of both Na+ - nitroprusside and methacholine. The response to methacholine was limited in both carotid allografts and control grafts probably explained by damage to the endothelial cells during explantation.

The contractile and dilatory responses were more substantial in the control carotid grafts (Fig 4).

Morphological and morphometrical analysis
Mean intimal thickness was less in the glycerol allografts in both proximal and midgraft segments compared to the UW preserved grafts albeit that this difference was statistically significant only.
Figure 4. Differences in isometric contractile and relaxation force responses (mN) assessed in ring segments of fresh carotid arteries (carotid control, n = 12) and glycerol preserved allografts (carotid graft, n = 10). Error bars depict SEM. KCl = after stimulation with 50mM potassium chloride, SNP = after addition of Na+ -nitroprusside (1.10⁻⁵ – 1.10⁻⁴M) to determine endothelium-independent relaxation, MET = after addition of methacholine (1.10⁻⁷ – 1.10⁻⁴M) to examine endothelium-dependent relaxation and PHE = after addition of the α₁-adrenoceptor agonist L-phenylephrine (1.10⁻⁷.5 – 1.10⁻⁴ M)

in the midgraft position (p < 0.001). At the distal anastomosis, the intima was thicker in the glycerol allografts (Fig 5, p = 0.02). As expected, the autologous vein grafts and control carotid artery segments showed only thin intimal layers. The results of media thickness are presented in figure 6. At all locations the glycerol allografts had the smallest thickness of media which was significantly different compared to the UW allografts (Fig 6, p < 0.01). Pooling of the results at all locations showed no significant difference in mean intimal thickness between glycerol allografts and UW allografts (34µm (SD = 5) and 37µm (SD = 4)). For the pooled results of media thickness, a significant difference (p < 0.001) was found between mean thickness of glycerol and UW segments (124µm (SD = 56) vs 161µm (SD = 4))

Scanning electron microscopy
The scanning electron micrographs of the UW allografts showed a confluent layer of endothelial cells somewhat higher compared to the control carotid artery endothelial cells (Fig 7A and B). The endothelial cells were partly shriveled up and became less strongly attached to the subendothelial medial layer (Fig 7B insert). Confluent intraluminal coverage was also determined in the glycerol preserved allografts. A neo-intima was formed (Fig 7C) and the intraluminal surface of the autologous vein grafts demonstrated a diminished profile compared to the arterial allografts as seen in Fig 7D. Some damage to the confluent layer of endothelial cells was seen as small cracks in the intima of the transplanted venous autografts (Fig 7D insert).
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Figure 5. Results of mean intimal thickness (µm) of glycerol preserved carotid allografts (gl, n = 14), carotid allografts preserved in University of Wisconsin solution (uw, n = 10), jugular venous autografts (au, n = 5) and fresh carotid arteries (ca, n = 5). Error bars depict SEM. prox = proximal part of graft, mid = middle part of graft and dist = distal part of graft.

Figure 6. Results of mean media thickness (µm) of glycerol preserved carotid allografts (gl, n = 14), carotid allografts preserved in University of Wisconsin solution (uw, n = 10), jugular venous autografts (au, n = 5) and fresh carotid arteries (ca, n = 5). Error bars depict SEM. prox = proximal part of graft, mid = middle part of graft and dist = distal part of graft.
DISCUSSION

This study demonstrates the feasibility of glycerol preservation of vascular allografts with diameters comparable to human peripheral arteries. No significant stenosis was observed in the glycerol allografts. When compared to UW preserved allografts, glycerol allografts demonstrate less intimal hyperplasia in midgraft segments and repopulation of the glycerolized tissue matrix by recipient cells resulting in renewed contraction and relaxation capability of the vessel wall after transplantation.

The bilateral carotid artery transplantation model used in the current study, is successfully used for the assessment of pseudo-intima proliferation, for examination of the effect of antiplatelet drugs, and for assessment of arterial conduits and intravascular thrombectomy devices (19-22). An important advantage of our model is the similarity of vessel diameter and hemodynamic properties of the carotid artery in the goat when compared to human peripheral arteries (23).
Limitations of the study include the time of follow up. A prolonged follow up period for up to 6 or 12 months would have facilitate the extrapolation to the clinical setting with patency rates after 1 or 2 years follow up. Although this had lead to high costs.

Another limitation is that we did not transplantate the upper or lower limb arteries. These are mainly involved in human peripheral arterial disease. Transplantation of leg arteries in an animal model is not favourable due to higher risk of infection and traumatic events which hampers wound healing.

During three months follow up, the mean diameter of the glycerol preserved allografts stayed close to the initial value of almost 6.0 millimeter. A significant increase in arterial diameter however, was shown in the UW preserved allografts which consistently increased after one month of implantation. The increase in diameter potentially leads to aneurysm formation and ultimately, vessel wall disintegration (24). In a review of explanted synthetic and biological grafts in clinical peripheral arterial reconstructions, aneurysmal degeneration was the reason for graft explantation in 72% of allografts used as a blood access for hemodialysis (25). In general, aneurysmatic dilatation develops in the long term, therefore we are cautious with final conclusions from our experiments because of the relatively short follow-up. Future research is necessary to study the long-term risk of aneurysmal degeneration.

Endothelial dysfunction followed by endothelial cell-leucocyte interaction, endothelial destruction and smooth muscle cell (SMC) loss are processes which play a central role in vascular allograft rejection and graft dysfunction (26;27). To overcome this cascade, re-endothelialization and neo-intimal formation, most likely the result of the proliferation of SMCs of recipient origin, is generated in transplanted vascular allografts (28). Functional endothelial cells and SMCs are necessary in maintaining a good vasomotor function as alterations in the nitric oxide-endothelin homeostasis play an important role in the development of allograft transplant vasculopathy (29).

In a previous study glycerol preserved allografts were transplanted in a rat aorta transplantation model. Anti-von Willebrand factor antibody immunostaining was used to assess endothelial graft coverage and anti-α-actin antibody to visualize vascular SMC. No differences were found in endothelial cell coverage and SMC repopulation between GL allografts and autografts after 3 months of follow-up. Given the available techniques in goats, it is not feasible to differentiate between persisting cells of the donor in the vascular graft after transplantation or ingrowing cells from the recipient. A mononuclear infiltration was observed only around the sutures of a GL preservated vascular graft (17). Therefore, we assessed repoplulation of the non-viable tissue matrix after GL preservation in our study, using the contraction and relaxation experiments.
GL allografts did respond to vasodilating and vasconstricting agents demonstrating neo-endothelial cell and SMC interactions resulting again in some of the original functionality. This means ingrowth of recipient endothelial and SMCs in the donor extracellular tissue matrix. GL preservation results in pyknotic nuclear cells and complete loss of contraction and relaxation capacity (16).

Bishop et al (31) reported ten days glycerol 98% preservation of venous allografts used as interposition graft in the common carotid artery in a goat model. Six months patency was 64% compared to 88% for autografts. Handling and suturing qualities were as good as untreated fresh vein and aneurysm formation in the vessel wall or at the anastomosis was not detected suggesting adequate strength and durability of the allografts. Although scanning electron microscopy and histology revealed endothelial disruption after preservation it apparently did not result in a sufficiently thrombogenic graft surface to compromise long-term graft function (31). Differences in patency rates between this experiment and the current study can, apart from the longer observation time (i.e. 6 months), be explained by a better compliance match between native artery and glycerol preserved artery compared to glycerol preserved vein.

Neo-intimal thickness was comparable at both proximal and distal anastomoses in both UW and glycerol preservation groups and was very limited in autologous venous grafts.

In contrast, glycerol allografts showed a significantly thinner intima in the midgraft segments compared to the UW allografts after three months follow-up. Although a short period of UW preservation preserves vasomotor activity after cold storage which means that endothelial cells and SMCs will survive the storage period to some extent, these cells will have sustained damage due to the 48 hours of cold ischemia (26). These injured cells induce cellular proliferation probably from surviving native graft SMCs, recipient endothelial cells from both anastomoses and circulating endothelial progenitor cells (32;33). Extensive neo-intimal formation in UW grafts can occur secondary to the immunological reaction to graft endothelial cells which results in chronic intimal injury and enhanced neo-intimal proliferation (34). The diminished neo-intimal formation in the glycerol preserved allografts in the current study is probably explained by the fact that glycerol preservation results in a non-viable extracellular tissue from which all living endothelial cells have been eliminated (16).

An intact intraluminal coverage by an endothelial monolayer in the transplanted vascular grafts is important in prevention of intravascular coagulation (35). In the current study this monolayer was present in the control carotid arteries and could also be demonstrated in the autologous vein grafts. Flat endothelial cells with a smooth surface and without pores and microvilli are criteria for cells in normal condition (36). Endothelial cells were flattened in the glycerol allografts too, comparable with the endothelial cells in the autologous veins. However, the endothelial cells preserved in UW seemed to have decreased in size and have lost cellular attachment. Endothelial cell remnants seen on top of the neo-endothelial cells in the glycerol
allografts suggest temporary luminal coverage by donor endothelial cells to enable recipient neo-endothelial cells to proliferate and constitute a new bond with the graft internal elastic lamina. GL-preserved arterial allografts can probably be used for small caliber vascular bypasses when AU specimens are not available. UW preserved allografts could only be preserved for a short period of time (1-2 weeks), whereas GL-preserved allografts could be stored for at least 3 months with maintenance of structural properties. In view of these prolonged storage opportunities, iliac and femoral arteries could be procured in multi-organ harvest procedures, preserved in GL and stored in a vascular tissue bank. The absence of aneurysmal degeneration and the lesser degree of intimal hyperplasia and inflammatory reaction in GL allografts, as compared to UW allografts, render GL allografts a feasible alternative to cold-stored vascular grafts.

In conclusion, glycerol preservation of arterial allografts in this large animal model of carotid artery transplantation, showed a promising patency rate after 3 months. Vessel wall diameter of the preserved allografts was maintained as well as several functional characteristics owing to repopulation of the vascular tissue matrix by host cells.

These results encourage us to devise a pilot study using glycerol preserved arterial allografts in a clinical setting.
Reference List


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