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Inhibition of vein graft remodeling and neo- intimal formation using a cobalt chrome external support

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ABSTRACT

Objective: Despite significant advances in the understanding of vein graft remodeling during the post-implantation, vein graft disease is still a major limitation of surgical revascularization. The study objective was to evaluate the performance of a new cobalt chrome external support device designed to mitigate vein graft remodeling and development of intimal hyperplasia.

Methods: Bilateral carotid interposition of reversed saphenous vein graft segments was performed in seven adult sheep. Following completion of the first anastomosis, randomization was performed to allocate the experimental and control grafts in each animal. Post-procedure, Doppler US was used to assess grafts lumen diameter at T0 and then 3-5 and 12-14 weeks after surgery. At 12-14 weeks, all sheep underwent angiography to assess grafts patency and lumen uniformity (coefficient of variance - CV) after which they were sacrificed, and all grafts were harvested for microscopic histological analysis.

Results: Baseline (T0) internal diameter was not significantly different between the supported and unsupported grafts. At twelve to fourteen weeks, the internal diameter of supported grafts remained unchanged and was significantly lower compared to the non-supported grafts (6.6mm±0.4mm vs. 12.8mm±4.0mm respectively, p= 0.0001). Percentage coefficient of variance (%CV) was 4.6% ± 4.3 in the supported grafts as opposed to average CV% of 14.7% ±6.5 in the non-stented group (p=0.011). Neointimal area was significantly lower in the stented compared to the non-stented group (1.4 mm2± 3.3mm2 versus 9.6mm2 ± 9.7mm2 respectively, p=0.009).

Conclusions: External support of vein grafts using a braided cobalt chrome external stent reduces early vein graft remodeling and mitigates the development of neointimal hyperplasia.

Key words: *Peripheral bypass, vein graft, intimal hyperplasia, graft patency, infrainguinal bypass, external support*

Introduction

The autologous vein bypass remains the most effective and durable revascularization strategy for patients with critical limb ischemia [1]. However, despite significant advances in the understanding of venous pathophysiology post-implantation, little progress was made in the clinical setting in which vein graft failure rate is still 30 - 50% within 3 to 5 years [1,2].

Early graft occlusion, within one month from implantation, is generally ascribed to technical or procedural related complications (e.g., kinking and twisting) or poor conduit quality. Late vein graft failure is attributed to the structural changes that occur in the conduit immediately post-implantation due to the exposure to

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the hemodynamics of the arterial circulation [3]. Vein graft remodeling includes an inflammatory response accompanied by the development of intimal hyperplasia which serves as the foundation for graft thrombosis and occlusive atherosclerosis [3,4]. Attempts to mitigate intimal hyperplasia in vein grafts have been the focus of intense clinical research. Most of the pharmacological therapeutic modalities have shown a limited effect in the clinical setting [2,5]. Recently, external mechanical supports have shown considerable promise in pre-clinical testing with significant mitigation of proliferative intimal hyperplasia achieved by reducing wall tension, improving lumen uniformity and creating a protective "neo-adventitia" layer, rich with microvasculature [6,7]. In the clinical setting, the same biological effects were observed in externally stented saphenous vein grafts twelve months after coronary artery bypass grafting (CABG) [8-10]. In addition, studies have shown that external reinforcement of varicose veins in peripheral bypass enabled the use of autologous tissue in patients with suboptimal conduit quality [11,12].

This study evaluated a novel cobalt chrome external support for peripheral vascular reconstruction. The objective of the study was to assess the device performance in mitigating vein graft remodeling and development of intimal hyperplasia 12-14 weeks post-implantation.

Methods

Seven adult female domestic ASSAF sheep weighing 74.5-83.5Kg formed the basis of this study. Surgical procedures were conducted at the Technion, Israel Institute of Technology, Faculty of Medicine, Haifa, Israel after obtaining approval from the institute's ethical committee for animal experiments. All procedures complied with the Animal Welfare Acts of 1966 (P.L. 89–544), as amended by the Animal Welfare Act of 1970 (P.L. 91–579) and 1976 (P.L. 94–279) and after obtaining approval from the institute's ethical committee for animal experiments.

The device evaluated is made from braided cobalt chromium- nickel-molybdenum-iron alloy fibers, forming a kink resistant mesh tube (FRAME, VGS - Vascular Graft Solutions, Tel Aviv, Israel), designed for external support of vein grafts in peripheral vascular reconstruction. The carotid artery interposition grafting model chosen for this study is commonly used for studying peripheral bypass [6] and assessment of vein disease development. The model allows the superficial position of the test article, without violating a major body cavity and enables monitoring with duplex ultrasonography.

Surgical Procedure

Following overnight fasting, animals were premedicated with Ketamine (10mg/kg i.v) and Xylazine (0.2mg/kg i.v) and were given a prophylactic dose of antibiotic (Cefazolin 1g i.v). After induction with Thiopental (10mg/kg i.v) and intubation, the animals were ventilated (Hallowell) artificially using a mixture of Isoflurane 1.5-3% and oxygen. An analgesic (Tolfine 4mg/kg i.m) was given 48h before opening the neck. Heparin 5000 units were administrated to all animals before carotid excision, and additional doses were given to maintain Activated Clotting Time (ACT) values above 300 seconds until completion of the surgical procedure. All animals were pretreated with Clopidogrel (225mg/d) 72 hours before surgery and during the follow-up period.

The greater saphenous vein was harvested from one of the hind legs through an uninterrupted incision. Vein calcifications and aneurysms were assessed, and external diameter was documented in three locations along the slightly inflated vein using a surgical ruler. Non-uniform veins or veins with diameter > 9mm were excluded and replaced with different and suitable vein segment. Side branches were ligated using 4-0 sutures, and the vein was preserved in heparinized saline. Following exposure of both common carotid arteries through a midline neck incision, a 3 cm carotid artery segment was excised from one side, and a 3-3.5cm venous segment was anastomosed in a reversed, end-to-end fashion with a running 6-0 polypropylene suture to the proximal side of the carotid artery. Following the completion of the proximal anastomosis, a randomization envelope was opened, and allocation of the experimental and control grafts (right or left) was determined. Distal anastomosis was completed similarly before the other carotid was excised and replaced with a second venous segment.

For the supported vein graft, an appropriate device model was selected according to the vein diameter, to avoid over constriction of the vein (maximum 18% di-

ameter reduction) and not less than the recipient carotid artery diameter, thus avoiding downsizing of the carotid artery. Mean external vein diameter at baseline was 6.3±0.5 mm (5.8 -7.3 mm). Selected external support device diameter was 6 mm for all supported grafts which complied with the principle described above. The axial force and radial force of the selected model were 0.00365 N and 71.848 N/m^2, respectively. The device length was cut to cover the entire length of the vein graft and a few mm of each side of the recipient carotid. After threading and expanding the device on the experimental graft, the distal anastomosis was completed (Figure 1). No fixation methods (i.e., sutures or glue) were used to attach the device to the graft. Once both grafts were fashioned and before surgical incision closure, Doppler Ultrasound (US) was used to verify adequate flow. All animals were monitored until awake and alert.

Follow up

During follow up period, all sheep were monitored daily for feeding (BAR test) and examined by a veterinarian once a week. Doppler US (Vivid I, Linear probe Duplex ultrasound system, GE, USA) was used to assess grafts patency and lumen diameter at three-time points: T0 (baseline- before neck closure), T1 (3-5 weeks post procedure) and T2 (12-14 weeks post procedure). At 12-14 weeks, all sheep underwent bilateral carotid angiography (Fluoroscopy machine: GE OEC 9900). Both supported, and non-supported grafts were assessed in all animals. Vein graft patency and lumen uniformity were evaluated using qualitative comparative analysis (QCA). Lumen diameter was measured at 5 points evenly spaced along the entire length of the inter-positioned venous segment. Measurements were calibrated according to the 6Fr diagnostic catheter used for the angiography. The coefficient of variance (CV), defined as standard deviation of lumen diameter divided by mean lumen diameter, was calculated for each graft to reflect lumen uniformity. After completion of the 12-14 weeks angiography, all animals were sacrificed.

Histologic evaluation

Following animal sacrifice, all grafts were macroscopically evaluated in situ and then harvested. Specimens were rinsed with 10% glucose and fixated with 4% formaldehyde at the biological pressure of 120mmHg. Grafts were photographed, fixated whole, and sent for

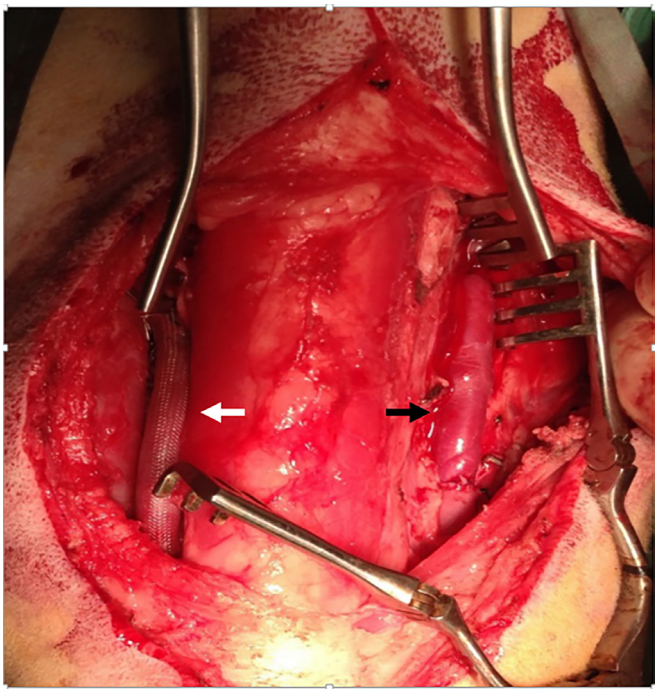

Figure 1. Sheep's neck after completion of venous interposition to the carotid arteries. White arrow - supported graft, black arrow - non-supported graft.

histopathology analysis (Charles River Laboratories, Inc. Maryland, USA). Specimens were initially radiographed by Faxitron (Faxitron Bioptics LLC, Tucson, AZ), a high-resolution cabinet x-ray system for both in-vivo and ex-vivo applications, to verify device integrity. Each specimen was sectioned at two locations along the vein graft, approximately 1 cm from each anastomosis. Two segments per each non-supported and supported graft were embedded in paraffin and methylmethacrylate (MMA) respectively. From each block, ~5μm sections were cut and stained with Verhoeff's elastin (VE). All MMA and paraffin sections were evaluated microscopically for morphometric evaluation. For each slide, the neo-intima and media layers were identified and measured (area in millimeters).

Inflammatory cell infiltration was microscopically assessed on hematoxylin and eosin (H&E) staining describing the number of inflammatory cells (neutrophils/lymphocytes) per High Power Field (HPF).

Statistical Analysis

Numerical variables comparing stented and non-supported grafts at any given time point were analyzed using the paired t-test. Vein diameter over time or over segments was analyzed using mixed model repeated measurements (MMRM). The model accounted for possible dependency between the measurements done

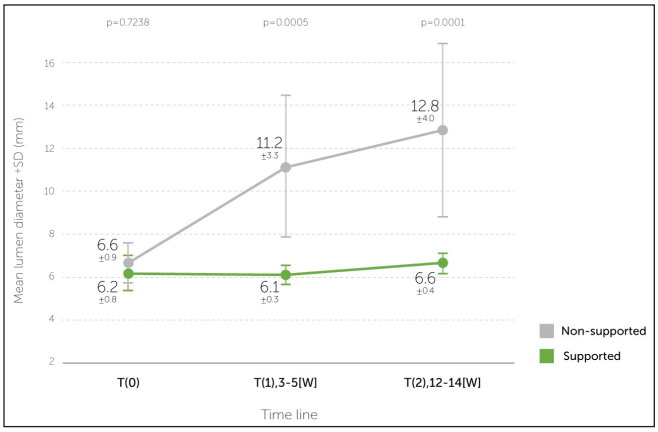

Figure 2. Vein grafts mean lumen diameter at different time points measured by Doppler US.

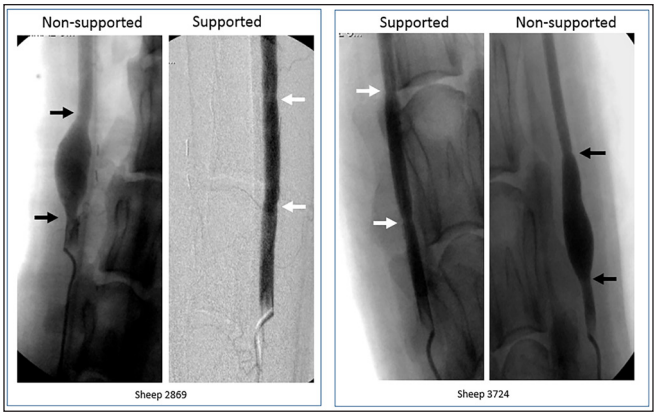

Figure 3. Angiographic images at T2 = 12 weeks for externally supported and non-supported vein grafts. Black (non-supported) and white (supported) arrows indicate the site of anastomoses.

within graft over time and between the measurements done on different grafts within the same animal. The coefficient of variance was calculated using t-test with equal variances to compare internal diameter variance of the experimental and control grafts. All tests were two-sided at a significance level of 0.05. Data were presented as mean ± standard deviation or percentage of coefficient of variance for graft uniformity evaluation. All statistical analyses were carried out using SAS® Version 9.4 under Windows® 2000 Terminal.

Results

Seven female domestic sheep successfully underwent bilateral interposition of two saphenous vein segments into each of the common carotid arteries. Four left, and three right-sided grafts were randomized into the treatment arm and were supported by the FRAME external support while the contralateral grafts served as control (non-supported). All procedures were performed by a vascular surgeon. One animal died three days post operation and was therefore not included in the comparative analysis. Postmortem analysis was performed, and the cause of death was determined to be aspiration pneumonia, likely related to the anesthesia and unrelated to the device. No physical or behavioral abnormalities were observed during the follow-up period for the remaining six sheep.

Assessed by Doppler US, baseline (T0) lumen diameter was found to be similar for the supported and non-supported grafts, (6.2mm±0.8mm vs. 6.6mm±0.8mm respectively, p= 0.72). At 3-5 weeks, the lumen diameter of supported grafts remained unchanged and was significantly lower compared to the dilated non-supported grafts (6.1mm±0.3mm vs. 11.2mm±3.3mm respectively, p= 0.005), with no further significant development at 12-14 weeks (6.6mm±0.4mm vs. 12.8mm±4.0mm respectively, p= 0.0001). The average lumen diameter of the vein graft at all three-time points is shown in Figure 2. At 12-14 weeks all supported, and non-supported grafts were patent on angiography with no significant stenosis. All devices were observed in place without any migration. Lumen uniformity defined by average CV was 4.6% ± 4.3 in the supported grafts as opposed to 14.7% ±6.5 in the non-supported group (p=0.011) (Figure 3). Table 1 summarizes the angiographic findings.

Histology

Grafts were examined macroscopically and microscopically. Faxitron radiography confirmed intact and non-deformed devices. Microscopic evaluation of inflammatory cells revealed minimal to mild infiltration of neutrophils/lymphocytes in the supported grafts (Table 2). Inflammatory cells adjacent to many of the device struts consisted of macrophages (and an occasional multinucleated giant cell). Significant reduction in neointimal area was observed in the supported grafts compared to the non-supported group (1.4 mm2± 3.3 mm2 versus 9.6mm2 ± 9.7mm2 respectively, p=0.009) (Figure 4). In addition, media area was smaller in

Table 1. Angiographic evaluation at 12-14 weeks post procedure.

	Supported	Non-supported	P value
Patent grafts	6/6	6/6	
Mean lumen diameter [mm]	7.9 ± 0.5	13.3 ± 4.4	0.028
Coefficient of variation (%CV)	4.6± 4.3	14.7± 6.5	0.011

Table 2. Inflammatory cell infiltration analysis.

	Supported	Non-supported
No inflammation	0/6 (0%)	6/6 (100%)
Minimal infiltration of few (<10) inflammatory cells per HPF	4/6 (67%)	0/6 (0%)
Mild infiltration of 10-50 inflammatory cells per HPF	2/6 (33%)	0/6 (0%)
Moderate (>50) to severe (>100) infiltration of inflammatory cells per HPF	0/6 (0%)	0/6 (0%)

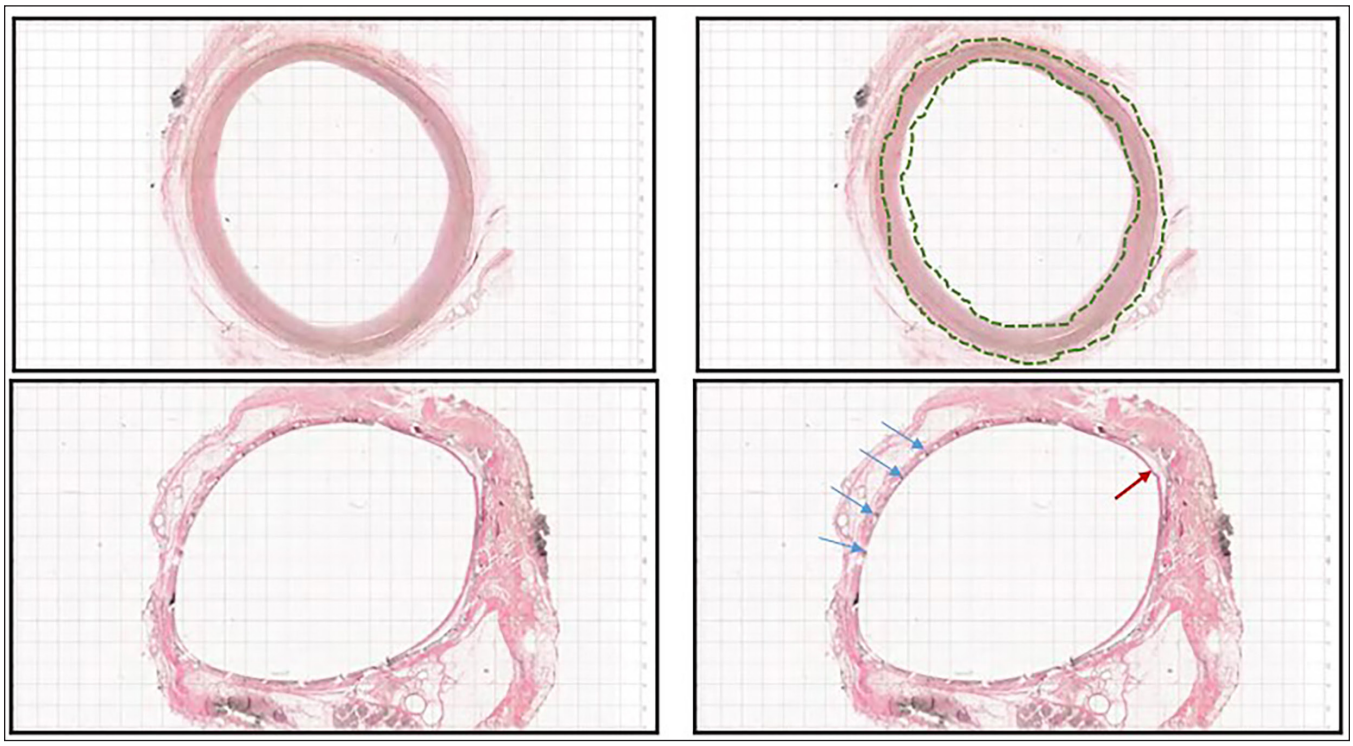

Figure 4. Histology images at 12 weeks: histologic cross sections with Verhoeff's elastin stain form distal 3rd of the non-supported graft (top) and proximal 3rd of the supported graft (bottom) from the same animal. Neo-intima area in the control graft is marked in green. Struts of the device are marked with blue arrows, and neo-intima (virtually single cell layer) is marked with red arrows.

Table 3. Histological analysis 12-14 weeks post procedure.

	Supported	Non-supported	% Difference	P value
Neo-intimal Area [mm^2]	1.4±3.3	9.6±9.7	86	0.009
Media Area [mm^2]	4.1±3.1	8.5±7.3	52	0.059

the supported grafts (4.1 mm2±3.1 mm2 versus 8.5 mm2±7.3 mm2, supported and non-supported grafts respectively, p=0.059). Histological Data is summarized in Table 3.

Discussion

This study strengthens and corroborates previous pre-clinical and clinical reports and demonstrates that external support of vein grafts with a braided cobalt chrome device can prove effective in mitigating vein graft remodeling. A particular strength of this study is the case-controlled model that, together with the randomization timing after completion of the first anastomosis, ensures minimal introduction of bias to the results. Inter-positioning adjacent venous segments, from the same vein, into similar carotid arteries in the same animal led to minimal differences in the baseline physiological parameters that may affect post-implantation vein graft remodeling.

The early phase of vein graft remodeling is dominated by luminal enlargement followed by a later phase of vein graft thickening and stiffening. In a clinical study of 96 lower extremity venous bypass grafts, the

mean increase in the lumen graft diameter was 21.6% one month after surgery, while initial shear stress was the single biggest predictor of lumen diameter change [13,14]. Luminal enlargement, associated with the exposure to the flow and pressure of the arterial circulation, lead to increased wall tension. As a reaction to the high wall tension, the vein graft compensates with a proliferative increase in wall thickness (intimal hyperplasia) and changes in wall composition, a process which takes place 1-6 months after implantation [13].

This study shows that use of an external cobalt chrome braided support affects both the early and the late phases of vein graft remodeling. At 12-14 weeks, no luminal enlargement was observed in the externally supported grafts compared to the control grafts, which doubled their lumen diameter, from 6mm to 12mm. In addition, intima and media area was significantly reduced in the externally supported group and in many cases, the intima layer was a single layer of endothelial cells without measurable thickness (Figure 4).

The type of inflammatory infiltrate found adjacent to the device struts is universally seen in association with implanted metal devices. The minimal presence of other types of inflammatory cell infiltrates indicates that there was no acute or chronic inflammation.

Prior attempts to externally support vein grafts involved the use of fibrin glue and sutures to fixate the external support to the vein graft [15,16]. Experimental data have shown that the application of fibrin glue on the external surface of vein grafts lead to aneurysmal degeneration and excessive intimal hyperplasia which may have jeopardized vein graft patency [17-18]. Recent clinical data showed that suturing and fixating an external support device to the anastomoses leads to early failure of vein grafts, most probably due to an acute constriction of the anastomosis site [15]. Application of the FRAME device does not require the use of fibrin glue or any other fixation mechanism post-deployment. Its design enables the surgeon to thread it over the vein easily and then cut it to the desired length. Once deployed, the device is designed to have radial elasticity and enough axial stiffness to maintain its length and diameter.

There are multiple potential effect modes of external support on the mechanisms which contribute to vein graft remodeling. Intima and media hyperplasia proliferation manifests cells from diverse origins, including peri-adventitial fibroblasts, bone marrow-derived progenitor cells, and smooth muscle cells. As many as 60% of the neo-intima comprises cells originating from outside the adventitia of the graft [19-21]. External support targets some of the key factors associated with the development of intimal hyperplasia such as high circumferential wall stress and disturbed flow patterns due to luminal irregularities. Mildly constricting the vein grafts with a mechanical support reduces the wall tension induced by the arterial pressures and prevents the non-uniform dilatation of the graft post implantation period [6,7]. Meirson et al. have shown that external support led to improved lumen uniformity of saphenous vein grafts 12 months post-implantation which was directly correlated with a significant reduction in oscillatory shear stress and the development of intimal hyperplasia [8]. The inadequacy of oxygen and nutrients in venous blood makes the supply from the vasa vasorum particularly important to the components of the venous wall. After harvesting, the perivenous vasa vasorum fails to function effectively and cells migrate towards the inner layers, where oxygen is diffusing from the arterial circulation. Pre-clinical research has shown that external support affects venous wall remodeling by facilitating adventitial neovascularization which is critical to prevent migration of cells from the media and adventitia towards the inner layers [22]. In addition, external support may have a role in redirecting vascular smooth muscle cell migration through a reversed chemotactic gradient. Neutrophils and monocytes that aggregate around the external support (in the context of foreign body reactions as also shown in our study) release chemo-attractive proteins that attract smooth muscle cells and fibroblast to the external support [23].

A notable limitation of the study is the animal model which does not mimic exactly the anatomical and physiological environment of the peripheral bypass graft. Technical aspects regarding the construction of peripheral bypass graft, couldn't be fully evaluated in a carotid interposition model. The length variability in the peripheral graft, the conduit's path within the lower limb and the differences in hemodynamics may have

both functional and technical implications on the performance of external support.

Compared with carotid interposition grafting model, peripheral human vein grafts are exposed to more moderate flow and moderate shear stress. Thus their remodeling entails less outward dilatation than observed in this study (non-supported vein grafts almost doubled their diameter). To some extent, the significant outward dilatation can also be attributed to the short length of the venous segments in this model. In longer segments, as used in clinical practice, one might expect a more longitudinal spread of the increased wall tension with less pronounced luminal enlargement. However, such significant dilatation can be seen in clinical practice, in cephalic veins response to the arterial environment with high flow and shear stress after the construction of arteriovenous fistula (AVF). Outward dilatation of cephalic veins results in an approximately two-fold increase in diameter in the first 3-6 months, accompanied by the development of intimal hyperplasia which ultimately leads to failure of the AVF [24].

While some mechanical variables such as acute kinking and external pressure from adjacent organs can be simulated in the lab, further optimization of the grafting technique and better understanding of the biomechanical effect of external support on vein grafts in the peripheral bypass requires further clinical research.

Additional vascular procedures, in which vein segments are used to bypass or reconstruct diseased artery, may benefit from the use of a kink resistant external support. For example, peripheral (popliteal) aneurysm repair usually involves venous segments subjected to arterial hemodynamics and undergoing shear stress and wall tension induced remodeling, amenable to prevention by external support.

In this pre-clinical study, we demonstrated that externally supporting vein grafts mitigates the pathological remodeling of vein grafts and the formation of intimal hyperplasia. Gasper et al. demonstrated that early remodeling was predictive of late vein graft failure [25]. If translated to the clinical setting, our results suggest that external support is likely to increase long-term graft patency. However, further clinical research is required to establish the role of external support in peripheral vascular reconstruction procedures in the lower limbs.

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Conflict of interest

Samy Nitecki and Rona Shofti have an ownership interest (stock options) in Vascular Graft Solutions. Liad Yosef is employed by Vascular Graft Solutions.

Matteo Tozzi – None

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