

A Shape Memory External Support to Improve Vein Graft Patency

Timothy C. Boire¹, Colleen Brophy², Hak-Joon Sung¹

Vanderbilt University ¹Department of Biomedical Engineering ²Division of Vascular Surgery.

Statement of Purpose: The human greater saphenous vein (HSV) is the most commonly used conduit for coronary artery bypass grafting (CABG) and the most effective conduit in infrainguinal peripheral bypass grafting. However, approximately 40% of vein grafts fail within 12-18 months because of intimal hyperplasia (IH), which is due to injury during harvest and preparation, ischemia due to loss of the vasa vasorum, and arterIALIZATION (i.e. changed hemodynamic environment) of the conduit. This leads to risky re-do operations and/or extensive, only temporarily-effective percutaneous intervention techniques, with increased risk of myocardial infarction, angina, limb loss, and death. External mesh supports applied to saphenous vein grafts have demonstrated promise to inhibit IH by promoting adventitial microvessel growth (i.e. neo-vasa vasorum formation). The materials used to date, however, are highly rigid and inflexible, in contrast to the compliant nature of the artery. This increases restenotic risks and precludes application to curvaceous arterial regions, including the anastomoses most responsible for vein graft failure. To address this issue, a mechanically compliant, biocompatible, bioresorbable, macroporous shape memory stent was fabricated that can be custom fit around the anastomoses. The stent circumscribes a thin layer of pro-vasculogenic hydrogel that further promotes neo-adventitial growth¹, in turn reducing IH.

Methods: For stent fabrication, 88%poly(ϵ -caprolactone)-co-12%(α -allyl carboxylate ϵ -caprolactone) (88%PCL-12%ACPCL) was chosen because it is highly malleable at CABG operating temperatures ($T_m = 33.1^\circ\text{C}$), and is biocompatible/biodegradable². Glass rods were dipped into a 10 wt/vol% polymer solution containing 3 wt/vol% DMPA and UV crosslinked (4.89 J/cm^2 , 18.1 mW/cm^2) to obtain a thickness of 1 mm. Pores were generated with an Epilog Laser Engraver (25% power, 100 Hz rep rate). HSVs were obtained from patients at VUMC according to IRB protocols. HSV samples were treated with external supports by first wrapping the HSV with an in situ crosslinkable, gelatin hydroxyphenyl propionic acid (GHPA) hydrogel (7 wt% GHPA; 0.01% H_2O_2) that possesses pro-vasculogenic properties^{1,3}, then with the porous shape memory scaffold (Figure 1A). IH was then tested in a well-established ex vivo model. Tissue and immunohistochemical changes were observed and compared to untreated (day 14) and baseline (day 0) controls. After 14 days, tissues (N=5) were fixed in 10% formalin, paraffin-embedded, sectioned, and stained with elastin to assess intimal, medial, and adventitial areas. Sections were stained for α -SMA to observe smooth muscle cell (SMC) migration and proliferation, and vWF to visualize endothelium and neo-vasa vasorum growth.

Results: Shape memory external stents were fabricated with 332 μm pores (Figure 1D). In HSV samples treated with the external support, there was a 92% reduction in

intimal area after 14 days of ex vivo culture compared to untreated controls (Figure 1B – C, yellow bars). Medial thinning was also observed, with an 86% decrease in medial area. Conversely, there was a 15% increase in adventitial area. Intimal, medial and adventitial areas in the stent-treated group were similar to baseline (day 0). Staining with α -SMA reveals fewer SMCs in the stent-treated samples (Figure 1E) compared to the untreated control (Figure 1F), indicating less proliferation and migration of SMCs into the intima. Staining with vWF revealed an intact endothelial layer in both treated and untreated groups, with more abundant staining in the adventitia indicating neo-vasa vasorum growth induced by the external support (Figure 1G).

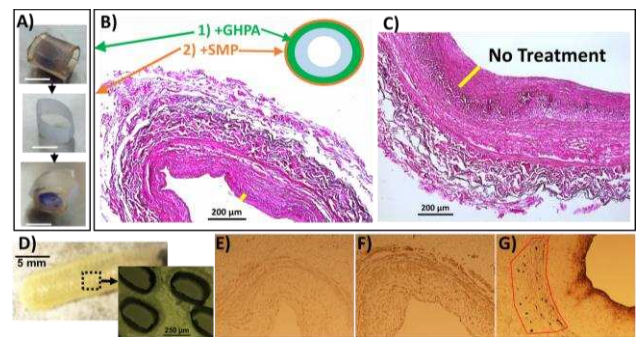


Figure 1: A) HSVs wrapped with 7%GHPA, 0.01% H_2O_2 , followed by 88%PCL-12%ACPCL. After 14 days ex vivo, HSV samples treated with B) external supports exhibited a marked reduction in intimal thickening (yellow bar) compared to C) untreated controls. D) Fabricated stent with macrosized pores (332 μm). E) α -SMA staining of stent-treated and F) untreated samples. G) vWF staining of treated groups, with neo-vasa vasorum encircled.

Conclusions: A mechanically-compliant, porous shape memory external support capable of wrapping around the anastomoses was fabricated. When HSVs were wrapped with a pro-vasculogenic hydrogel encircled by the shape memory stent, a reduction in intimal and medial thickening was observed, with an increase in neo-vasa vasorum growth. This demonstrates a promising effect of this support to reduce IH and improve vein graft patency in vascular bypass grafting procedures by positive remodeling. Future work will involve more histological, protein, and chemokine analysis of HSVs on each day to characterize the SMC phenotypic regulatory and signaling mechanisms behind IH reduction. HSV morphometric and phenotypic changes will also be evaluated in an ex vivo anastomoses model to determine support effects in this IH-prone region. An in vivo porcine model of saphenous vein to carotid interposition grafting will be conducted to validate these findings.

References:

- [1] Lee SH. Adv Func Mat. 2014; 2(41), 7109 – 7113.
- [2] Boire TC. Biomaterials (Under Revision). 2014.
- [3] Lee Y. Jrn of Mat Chem B. 2013; 1(18), 2407 – 2414.