Rationale and practical techniques for mouse models of early vein graft adaptations

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Mouse models serve as relatively new yet powerful research tools to study intimal hyperplasia and wall remodeling of vein bypass graft failure. Several model variations have been reported in the past decade. However, the approach demands thoughtful preparation, selected sophisticated equipment, microsurgical technical expertise, advanced tissue processing, and data acquisition. This review compares several described models and aims (building on our personal experiences) to practically aid the investigators who want to utilize mouse models of vein graft failure. (J Vasc Surg 2010;52:444-52.)

Clinical Relevance: **Surgical revascularization via vein grafting offers immediate and often dramatic end organ benefit. However, substantial percentages of vein conduits placed develop stenosis or fail, often early. Mechanistic studies of the complex interplay between the biologic and physical forces that drive failure have been hampered by limited quantity and quality of clinical specimens, and the inability of systems such as computer models and cell culture to mimic the clinical circumstance. This review summarizes the power and limitations of mouse vein graft models, and it includes practical experience-based advice for researchers aiming to utilize this tool.**

Surgical bypass via autologous vein stands as an evidence-based treatment of choice for selected patients with infrainguinal lower extremity or coronary occlusive disease;[1] thus, over half a million vein grafts are implanted annually in the United States. However, contemporary data show that almost 40% of lower extremity vein bypass grafts develop occlusive lesions or fail within a year,[2] and almost half of cardiac bypass patients will lose (≥75% stenosis) a vein graft within a year.[3] These failures result in recurrent end-organ ischemia, complex (and expensive) redo revascularizations, and not infrequently loss of human limb or life.

Intimal hyperplasia and negative (inward) vein graft wall remodeling are the main culprits of vein bypass graft failure. The former has been intensively studied for decades,[4-6] while the latter has only recently triggered research interest.[7,8] Since arterialized vein conduit tissue is rarely retrieved from patients, and due to the inability of contemporary cell and tissue culture approaches to mimic the multifactorial events of early vein graft failure, animal models serve as an essential tool to explore the mechanisms of vein graft adaptations.

There are many animal models that simulate arterialized venous bypass graft failure, eg, murine,[9-15] rattus,[16] rabbit,[17,18] canine,[19] porcine,[20] monkey,[21,22] and baboon.[23] Since the development of knockout and transgenic techniques, the use of mice in vascular research has boomed over the last two decades. With these approaches, researchers have tools to study the in vivo function of a specific gene product, while avoiding the difficulties associated with the use of antibodies or receptor agonists/antagonists (such as nonspecificity, immunoreactivity, dosing and tachyphylaxis). Additionally, the vein bypass graft model in mice also serves as a platform to test the influences of factors such as diseases, inflammatory states, and hemodynamic changes on vein graft wall adaptations.

This review will summarize the advantages and drawbacks to current mouse models of vein graft adaptations (Table I), compare the technical variations in mouse vein graft constructions, and provide a practical guide for utilization of this species for surgical vein bypass investigations. Investigators interested in exploring the use of animals for research should familiarize themselves with federal laws (the Animal Welfare Act of 1966 and its amendments), the Guide for the Care and Use of Laboratory Animals (National Research Council), NIH Animal Research Advisory Committee Guidelines,[24] and appropriate local laboratory animal welfare guidelines.

GENERAL TECHNICAL CONSIDERATIONS

Like most mammalian models of vascular diseases, in vivo mouse studies hold many confounding factors that contribute to observed variations in the vein graft adaptations (eg, amount of intimal hyperplasia), although most of these are not well documented for mice in the formal research literature. In our experiences, these include the surgeon's technical skills, the level of sterility within the operative field and subsequent local/systemic infection and inflammation, procedural time, ischemia time of the vein

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Table I. Mouse vein graft model advantages/disadvantages

Advantages	*Disadvantages*
• The most commonly used mammalian model organism, with a robust existing literature • Advanced genetics (mouse genome has been sequenced) and array of mice available • Established models of human disease, such as hypercholesterolemia, diabetes, and obesity • Less sentient than other available animal vein graft models	• Many murine models are new and lack a long-standing track record
• Relatively similar to humans in anatomy, physiology, and genetics	• As with all nonhuman research, applicability to the human situation may be limited
• Technological advances allow physiologic monitoring, such as flow rate and blood pressure monitoring	• Monitoring and measuring may lack resolution in small mammals • Small-scale instruments and monitoring devices can be relatively expensive
• Small, easy to maintain and handle, low housing costs • Have a short generation time, reproduce quickly and prolific • Low doses/volumes required for test solutions (eg, antibodies, gene therapy vehicles, pharmacologic compounds)	• Surgical procedures can be difficult to complete and reliably reproduce due to the small size of the murine vasculature • Available tissue quantities for assays are small • Limited volume of intimal hyperplasia in wild-type mice can make identification of preventative therapies difficult
• Wide availability of reagents for use with murine tissue	• Antibodies are often of murine origin

segment, vein desiccation, physical trauma (careless dissection or over-stretching of the vein or recipient artery, etc.), artery clamp times and end-organ ischemia (especially for aorta and common femoral artery models), total blood/fluid loss and replacement, and usage of heparin, etc. Among these, the surgeon's technique (especially minimization of physical vein endothelial trauma and the variation of hand-sewn anastomotic diameter) and ischemia/desiccation of the vein segment appear to be major contributors to the variability in early vein graft wall adaptations. For the novice microsurgeon attempting to master these complex models, it is recommended that practice time be completed to reach the plateau phase of the learning curve prior to engaging in any formal studies. The actual individual investigator's time to approach the learning curve plateau is quite variable (estimated 20-60 surgeries) and depends largely on the training environment and learner's original level of microsurgical technique.

Equipment. Basic microsurgical equipment is required for successful completion of these models. This includes an environment-controlled laboratory facility with a stable table and chair, autoclave/dry sterilizer, a set of high-quality, well-maintained microsurgical instruments, 5-0 to 12-0 sutures, and an operating microscope with high-intensity operating lights. The high-quality microsurgical operating microscope stands as a central component to the equipment. We utilize a Zeiss binocular, dual-headed OPMI-MD surgical microscope on S-5 Floor Stand (Carl Zeiss Inc, Germany), with T2 digital SLR camera/camcorder system (Fig 1, *A*). The magnification can be altered from 4-fold up to 24-fold. X-Y-Z adjustable foot control aids in precision and sterility, and a large depth of field (which is absent on some dissecting microscopes) is useful.

Intraoperative strategies. The surgical procedure should be performed under aseptic conditions. Mouse skin preparation (hair removal and scrubbing with povidone-iodine or other disinfectants) and sterile draping (Fig 1, *A*) are suggested.

Utilization of heparin is variable in published reports. We utilize heparinized saline (100 IU/mL) as flush solution only. Fixed positioning of the inflow and outflow artery ends can be achieved by microsurgical approximator clamps or simply securing two Micro Clips (Roboz Inc, Gaithersburg, Md) via a double-looped (easily adjustable) 4-0 suture around the clip handles.

Immediately after vein graft construction, patency can be determined by the pulsation of vein graft and distal artery, blood flow observation through the thin vein graft wall, gentle empty-and-refill (strip) test on the inflow or outflow artery (not recommended on the vein graft), and intraoperative flowmetry (we utilize a Transonic TS420 flowmeter with 1PRB flowprobe, Transonic Systems Inc., Ithaca, NY) or ultrasonography.[11] Simple judgment by turgidity of the vein graft is not reliable.

Perioperative strategies for anesthesia and analgesia. Since vein graft placement is a major survival surgery with prolonged operative time, use of a continuous inhalant anesthesia system (eg, isoflurane via a calibrated vaporizer, with scavenging devices) is recommended rather than injectable approaches. Some researchers employ an "open", noncalibrated method (bell jar or nose cone), which presents a challenge when attempting to control the agent concentration and anesthetic depth. Frequent monitoring of physiologic parameters such as respiratory rate and pain reflex is crucial. Prevention of hypothermia (via 37°C heating pad and lamp) and perioperative systemic fluid therapy minimizes anesthesia-related complications

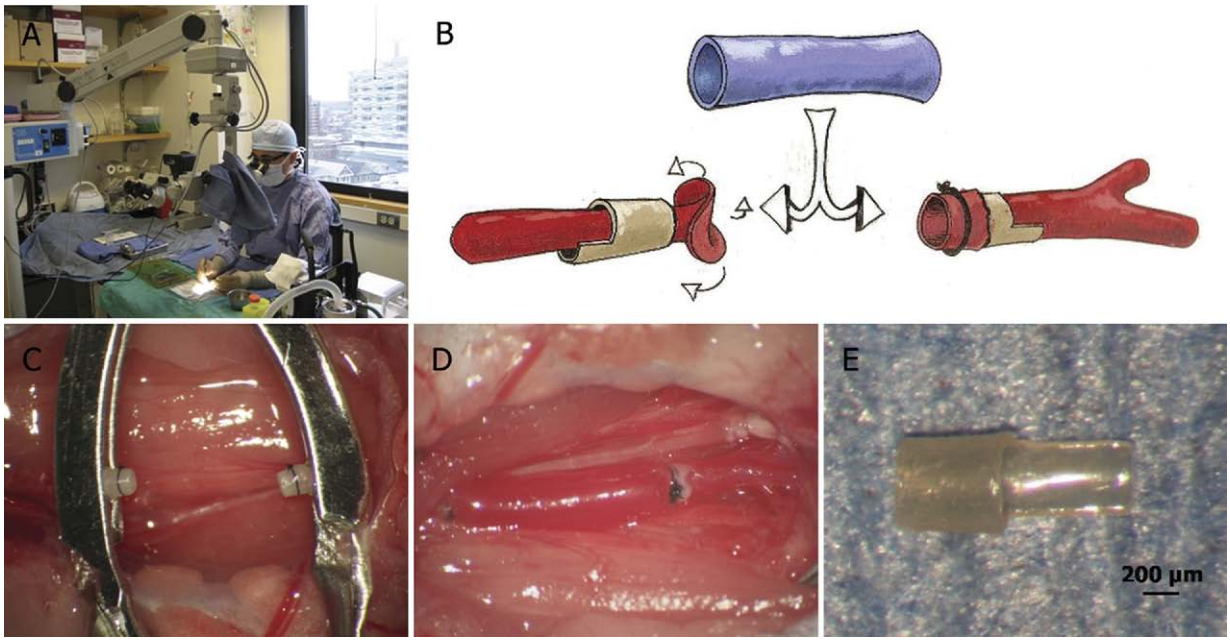

Fig 1. Cuff-technique mouse vein graft model. **A,** An example of a rodent survival operating suite with operating microscope and table-top small animal anesthesia system. **B,** Schematic representation of the cuff-technique vein bypass graft model. **C,** Two everted and secured carotid artery ends. **D,** Completed mouse carotid interposition vein graft. **E,** Hand-made polyetheretherketone anastomotic cuff with handle.

and shortens recovery time. An anticholinergic drug (such as glycopyrrolate or atropine) to reduce secretions in the respiratory tract is recommended, and we administer an analgesic agent (buprenorphine) at the time of surgical recovery and via schedule for 48 hours postoperatively.

MOUSE VEIN BYPASS GRAFT MODELS

Cuff technique for interposition graft. Zou et al[9] first described a mouse vein graft model completed by the cuff technique, which has been adopted or modified by several research groups (Fig 1).[25-30] In brief, the right common carotid artery was gently mobilized free from surrounding connective tissues as far distally and proximally as possible. It was then ligated with sutures at the midpoint and divided. After controlling the inflow and outflow arteries via clamps placed at the premade polyethylene cuffs' handles, the ligatures were removed, and the proximal and distal artery ends were everted over the tubular body portion of the cuffs, which had a 0.65-mm outside diameter (OD) and a 0.5-mm inside diameter (ID). The vein segment (from separate donor supradiaphragmatic inferior vena cava (IVC) or autologous external jugular vein) was then sleeved over the artery cuffs and secured into position with fine ties (as shown in Fig 1, *B, C,* and *D*). Mortality rate has been reported as 5.3%; patency rate at harvest time achieved 100%. Mean intima and media thickness (day 28, male C57BL/6 mice) was ~215 μm, though our group has not observed as thick of a vein graft wall with this approach (we observe typically about 50 μm average intimal thickness and 100 μm average wall thickness).

Cuff selection may be an important factor in this model. Zou chose polyethylene tubing (OD, 0.65 mm; ID, 0.5 mm) for 3-month-old mice. We find this material to be relatively soft and easy to distort if uneven force is exerted during artery eversion. The size is also relatively large for our 8-10-week-old (20-24 grams) mice. Diao et al reported carotid ID at 0.35 ± 0.02 mm (8-10-week-old, male C57BL/6J mice);[14] we also reported a similar result.[31] For the cuff material, we prefer an autoclavable polyetheretherketone extruded tubing (OD, 0.51 mm; ID, 0.41 mm; from Zeus Inc, Orangeburg, SC) (Fig 1, *E*).

Finally, 9-0 monofilament nylon suture performs well for ties, and 6-0 vicryl (Ethicon Inc, Somerville, NJ) for incision closure.

Hand-sewn techniques for interposition graft. Using an end-to-side anastomotic method, Zhang et al[11] transplanted a 10-mm-long donor's IVC segment to a recipient's common carotid (both from 17-20 grams male C57BL/6J mice) and secured each anastomosis with 8 to 12 continuous stitches of 11-0 nylon suture. The carotid segment between the IVC anastomoses was then ligated at both ends and cut. Operative time averaged around 20 minutes for IVC harvest and 90 minutes for carotid interposition grafting. Mortality rate was ≤10%, with a reported patency rate of >95%. Mean wall (medial + neointimal) thickness (day 28) was 91 μm.

Cooley[12,32] described a more delicate autograft model. Under ×60 magnification, a branch of the external jugular vein (2 mm in length) was dissected and transplanted into the femoral artery using 6 to 10 interrupted stitches of 11-0

Table II. Comparison of common mouse vein graft models

	Zou's[9] (cuff technique, IVC or jugular to carotid, end to end)	*Zhang's[11] (sewn, IVC to carotid, end to side)*	*Cooley's[12] (sewn, jugular to femoral artery, end to end)*	*Diao's[14] and Salzberg's[15] (sewn, jugular or IVC to aorta, end to end)*	*Shi's[10] and Sakaguchi's[13] (vein patch technique, jugular to carotid or aorta)*
Technical challenge	++	+++	++++	+++	+++
Relative procedure duration	++	++++	++++	++++	+++
Extensive bleeding risk	+	+++	++	++++	+++
Risk of thrombosis	+	++	++++	++	+++
Relative mortality	+	++	+++	+++	++
Reproducibility	+++	++	+	++	++
Clinical relevance	++	+++	++++	+++	++
Other considerations	Foreign body (cuff) response at ends		Short vein graft (2 mm)	Low neointimal volume	Not true vein graft

IVC, Inferior vena cava.

or 12-0 nylon suture per end-to-end anastomosis. Mortality rate was 15.9%, with patency rate at 81% on day 30. Mean wall thicknesses were 103 μm (proximal), 49 μm (middle), and 58 μm (distal).

Grafts to the abdominal aorta have also been reported. Diao et al[14] transplanted a 5-mm-long external jugular vein segment into autologous infrarenal aorta. Six or seven interrupted 11-0 nylon stitches at each end-to-end anastomotic site were employed. With this model, average aorta clamping time for male C57BL/6J mice was 68 minutes. Mortality rate was 11.4%; patency rate on day 28 was 100%, and mean wall thickness (day 28) appeared to be ≤60 μm (calculated from their representative images and graph).

Finally, Salzberg et al[15] utilized a similar end-to-end model but from the donor's IVC to the recipient's infrarenal abdominal aorta. Average aorta clamping time for male C57BL/KsJ mice was 30 minutes. Mean neointimal thickness (1 month postoperation) for this strain appeared to be ≤60 μm based on their data and representative images.

Hand-sewn technique for vein patch. In an attempt to mimic the events of the early vein conduit or an endarterectomy reconstruction[33-36] and building on a method employed in larger animals,[37] Shi and colleagues[10] described a vein patch as a surrogate for vein graft tissue. They harvested a ~5-mm-long external jugular vein (from 7-12-week-old male C57 BL/6 mice), cut open the conduit and trimmed it into an oval shape, and then used the patch to repair a surgically created defect in the ipsilateral carotid artery by a hand-sewn technique with 11-0 continuous suturing. The average time from venous patch harvest to common carotid artery reparation took about 40 minutes. The overall success rate was 92%. From the reported representative images, this model could induce obvious neointimal formation and wall thickening (day 20). Sakaguchi and associates[13] have reported an application of this technique to create a model that used a jugular patch to repair an abdominal aorta defect.

Table II summarizes the comparison of these mouse vein graft models, drawing upon the currently published literature and our personal microsurgical experiences (including over 400 mouse vein grafts).

MODEL VARIATIONS/MODIFICATIONS

Selection of a mouse strain and genetic background. Mouse strain has a significant impact on the vascular response to injury, and this should be taken into consideration when selecting a particular strain of mice for study. While there exists limited information on differences in susceptibilities to intimal hyperplasia[38] or negative remodeling in mouse vein graft models, data obtained from arterial studies may serve as a useful baseline.[39,40]

One of the advantages of working with mice is the vast array of transgenic and knockout animals available that simulate and facilitate understanding of human diseases. For example, ApoE-deficient mice were utilized to study hypercholesterolemia,[41] while $lepr^{db/db}$ mice served as a model for type 2 diabetes mellitus.[15] These genetic backgrounds can be combined with the mouse vein graft models to provide a wealth of information about the mechanisms of vein graft failure in different pathological settings.

Adjunctive hemodynamic manipulations. In addition, hemodynamic manipulations can also be utilized to study the influence of pressure and flow perturbations on vein graft adaptation. Wall tension is known to impact vein graft wall adaptations,[42,43] but largely due to their small size, invasive pressure measurements along mouse vein graft constructions have not proved reliable to date.

Conversely, flow manipulations in the mouse vein graft model have been reported. The mouse distal common carotid artery has two major branches, the internal carotid and external carotid. In addition to the presence of branches, they may be distinguished by size, with the internal carotid artery having a slightly larger diameter than the external carotid artery. The occipital artery, a small branch originating from the external carotid or the bifurcation, travels with the internal carotid. The superior thyroid artery is a very small branch arising from the external carotid artery (Fig 2).[44]

Osterberg and colleagues[45] employed high-flow and low-flow vein graft models (cuff technique) with 26-36 grams male C57BL/6 mice. By ligating the contralateral common carotid artery, they were able to induce a 20%

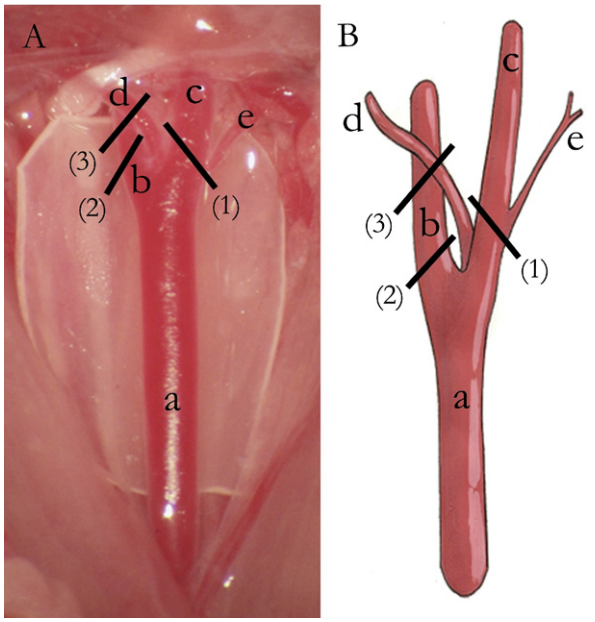

Fig 2. Mouse carotid artery anatomy and partial ligation methods **(A,** Photographed right carotid anatomy [*cut surgical glove background*]. **B,** Schematic representation). **a,** Right common carotid artery. **b,** Internal carotid artery. **c,** External carotid artery. **d,** Occipital artery. **e,** Superior thyroid artery. **(1),** Ligation of external carotid artery, including superior thyroid artery but not occipital artery. **(2),** Ligation of internal carotid artery. **(3),** Ligation of internal carotid artery plus occipital artery.

higher vein graft flow rate (average baseline blood flow at 1.0 mL/min) immediately after ligation, and a 1.1 mL/min average value at day 42 in the high-flow group. With ligation of the ipsilateral external carotid artery in the low-flow group, a 50% immediate decrease in flow rate was achieved, and it became 0.4 mL/min at day 42. The neointimal area in the low-flow grafts was 74% larger than that of high-flow mice at day 42, with mean intimal thickness of ~55 μm vs ~33 μm, respectively (calculated from graphs in their report).

Manipulation of vein graft wall shear stress changes vein graft neointimal hyperplasia.[46,47] We have completed various ligations of carotid branches to alter the flow rate. Ligation of the internal carotid artery plus occipital artery yielded an immediate 52% decrease in flow rate (1.18 ± 0.14 mL/min vs 0.57 ± 0.08 mL/min, control vs ligation, respectively) and a 73% decrease (1.31 ± 0.06 mL/min vs 0.36 ± 0.04 mL/min) at harvest (day 28). This method increased intimal thickness by 33% (50.2 ± 3.3 μm vs 66.9 ± 4.9 μm, Fig 3, *A* vs Fig 3, *B*, respectively). Ligation of both the external and internal carotid artery (leaving only the occipital artery patent) resulted in an immediate mean flow rate ≤0.1 mL/min (n = 6). However, this led to a high rate of graft occlusion, as only one of three grafts were patent at day 14, and three of three were occluded at day 28. The patent vein graft did show tremendous intimal hyperplasia (Fig 3, *C*).

The above results demonstrate the importance of various hemodynamic altering techniques for the wall adaptation of vein grafts. Attempts to ligate only the external carotid, only the internal carotid, or a combination of the internal carotid plus occipital artery (Fig 2) produced limited flow decreases, and consequently, only modest intimal hyperplasia was observed. Conversely, combining external carotid and internal carotid artery ligation (with only occipital outflow) too severely restricted flow, with exorbitant intimal hyperplasia, making this manipulation unpractical.

SPECIMEN PROCESSING AND ANALYSIS CONSIDERATIONS

Financial and labor investments in complex mouse surgical models are high, thus thoughtful and meticulous specimen harvest and processing are paramount. Tissue segments intended for frozen section histology or molecular analyses should be harvested fresh, although the frozen method for optimal morphologic analysis of a vein graft is not recommended because of the compromised anatomic preservation. We prefer whole animal perfusion fixation (by 10% formalin or 4% paraformaldehyde) under physiologic mean arterial pressure (~100 mm Hg) with intravascular access via the left ventricle or aortic arch. The right atrium or supradiaphragmatic IVC can be cut as the outflow tract of fixative fluid.

The intimal hyperplasia formation along the vein graft is not uniform: it is usually the thickest at the proximal, thinnest in the middle, and intermediate at the distal segment of the graft.[11,12,14] This observation is also confirmed by our morphological analyses on serial cross-sections (data not shown) and longitudinal sections (Fig 4) of the mouse vein grafts. Because of this variation, meticulous localized sectioning and comparison of specific segments of the vein graft is important. Using a landmark (such as cuff edges in cuff technique model or anastomotic sutures in hand-sewn models), paraffin sections are obtained at 50-to 200-μm intervals, and computer image processing is employed to translate these into quantified morphologic endpoints such as intimal thickness, wall area, and lumen narrowing.

The microscopic anatomic definitions of mouse vein graft wall and artery wall do not match very well. At least for the common mouse strains that we have worked with (C57BL/6J and B6129SF2/J), the only obvious elastic lamina of the vein graft is recognized by us as the internal elastic lamina because only a single (endothelial) cell layer covers it (Fig 3, *F*), and α-actin-positive cells appear beyond it (Fig 3, *G*) in the wall of mouse IVC. The tunica media of mouse vein graft could be obscure because of the early smooth muscle cell loss[45] but may still present in some cases (Fig 3, *H*). The mouse vein graft wall does not have a well-defined external elastic lamina, thus the evaluation of the tunica media and tunica adventitia requires a different method. Some authors utilize the vasa vasorum as a landmark to discern the interface between the media and adventitia.[9,11] We find this is difficult since the vasa vasorum may not always be present or associated with the true

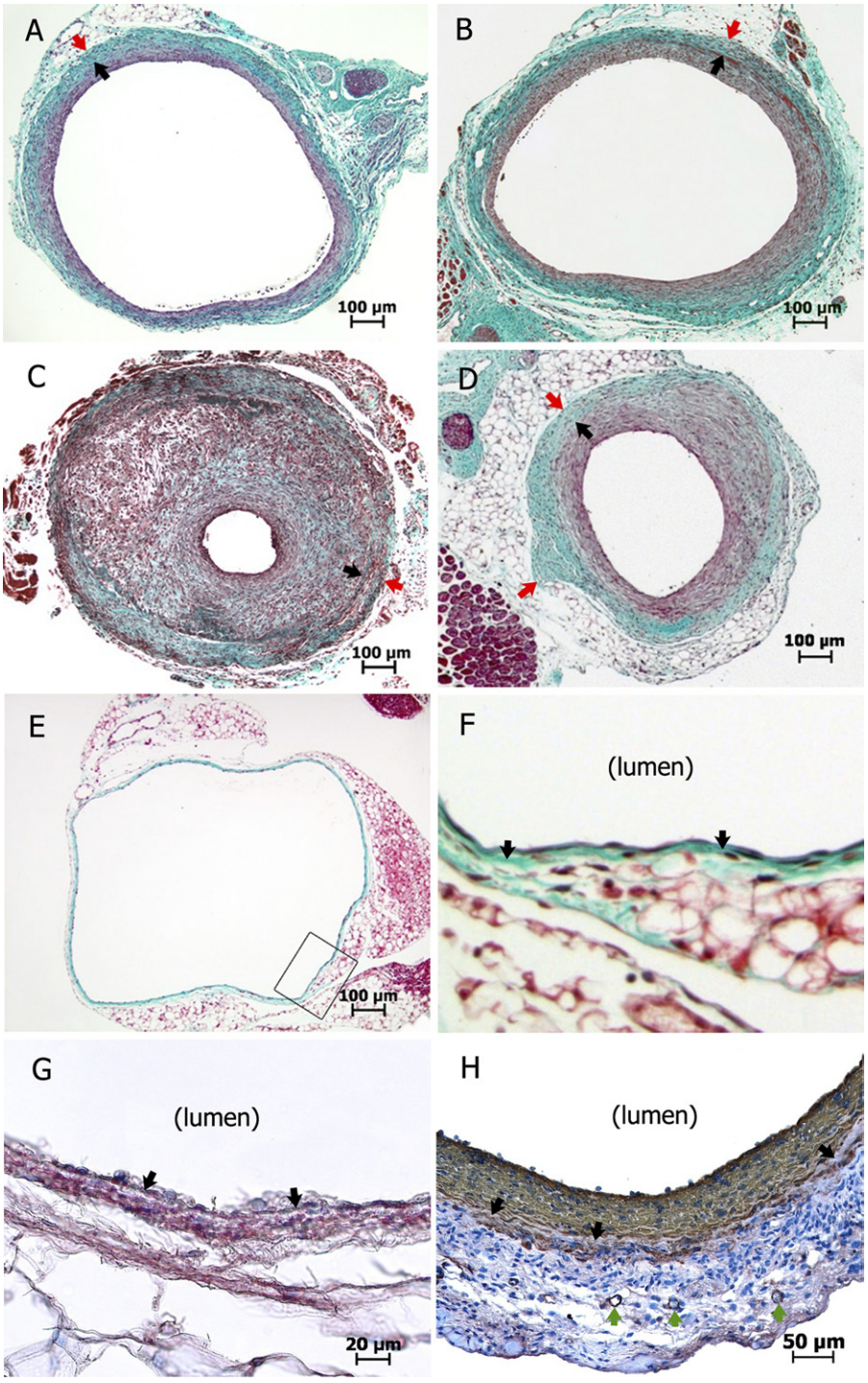

Fig 3. Masson trichrome staining **(A-F)** and α-actin immunohistochemistry staining **(G, H)** of cross-sections of mouse vein grafts/vein. *Black arrows* depict the internal elastic lamina **(A-D, F-H)**; *red arrows* show the tunica adventitia/perivascular tissue boundary **(A-D);** and *green arrows* show the vasa vasorum **(H)**. **A,** Normal flow vein graft at day 28. **B,** Vein graft with distal arterial partial (internal carotid + occipital artery) ligation at day 28. **C,** Vein graft with distal arterial partial (external carotid + internal carotid) ligation (leaving the occipital artery patent) at day 14**. D,** Negative wall remodeling in a mouse vein graft at day 28. **E,** Normal IVC. **F,** Enlarged area defined by the *black box* of Fig 3, *E.* **G** (*normal IVC*) and **H** (mouse vein graft at day 28), note some *rose-red* or *brownish-red* positive expression of α-actin in the tunica media (beyond the internal elastic lamina).

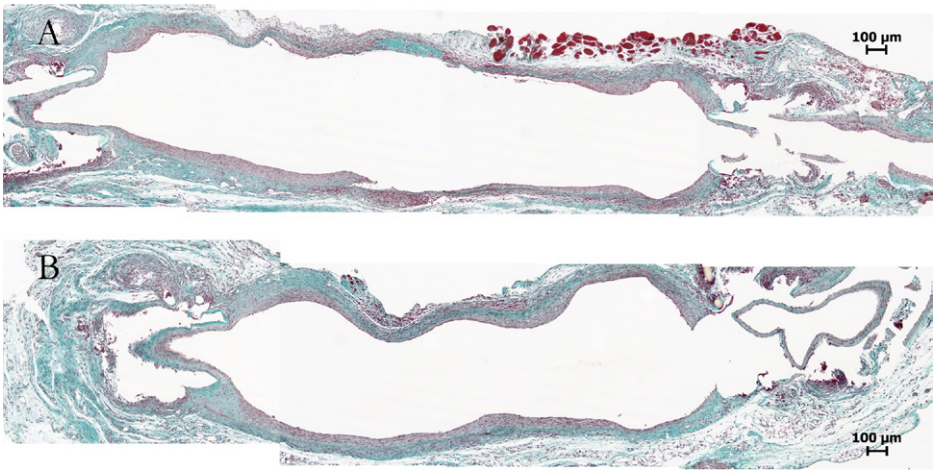

Fig 4. Masson trichrome staining of two longitudinally sectioned mouse vein grafts (cuff technique, cuffs were removed at ends, leading to artifact). Note variations in intimal thickness along the length of the graft.

media/adventitia interface (Fig 3, *H*). While the tunica adventitia has a relatively clear boundary with the surrounding looser connective tissue, it is not always round (as shown in Fig 3, *D*) and should not be confused with the external elastic lamina. To circumvent these issues, our practice is to combine the "media + adventitia" layers for morphological analysis.

Finally, similar to the clinical setting,[8] positive or negative (Fig 3, *D*) vein graft wall remodeling can occur. A single parameter, such as intimal area or thickness, cannot adequately describe total wall adaptation. For example, the grafts in Fig 3, *B* and Fig 3, *D* have similar intimal areas, but there are obvious differences in intimal thickness. Thus, histopathologic analysis of the vein graft tissue should not be confined to just the intimal thickness or area but also incorporate other parameters such as calculated ideal lumen area, total wall thickness or area, length of the internal elastic lamina in the perfusion-fixed section, and ratios among these parameters.[48]

MOUSE VEIN GRAFT LIMITATIONS

Current mouse vein graft models hold disadvantages. In most wild-type mice, there is limited neointimal formation, which hampers efforts to identify therapies to attenuate intimal hyperplasia. Several possible reasons contribute to this limitation. Our six-month mouse vein grafts did not show exorbitant neointimal formation (data not shown), and this suggests that simply extending the observation period does not resolve this limitation.

Normal mouse IVC has a very thin wall (average wall thickness is 12 μm, distended with arterial pressure, from male C57Bl/6J mice at age 9 weeks): one cell layer thick tunica intima, one elastic lamina, just one or two cell layers in the media + adventitia (Fig 3, *E, F,* and *G*). This renders early histologic evaluation extremely challenging.

Also, in mouse vein graft intimal hyperplasia, participation of graft extrinsic cells appears to be significant. A certain portion of neointimal cells and repopulated endothelial cells originate from non-wall origin (such as bone marrow),[49-52] and we do not know if such processes occur in the human scenario. Cells of various origins may respond differently to therapeutic agents.

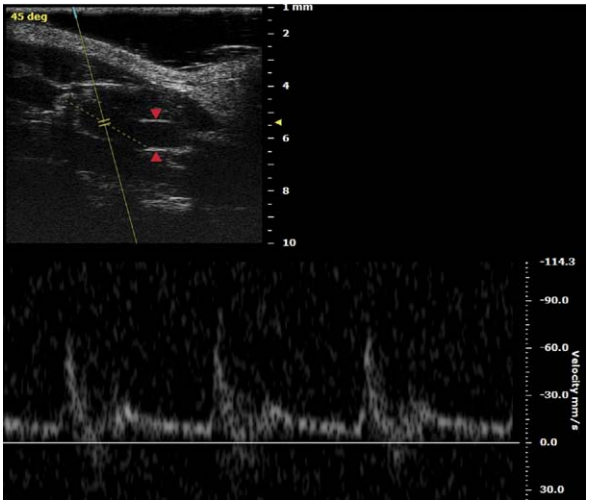

Fig 5. Upper left: Duplex ultrasound scanning of mouse right carotid vein graft model (cuff technique), taken by Vevo 2100 Imaging System (VisualSonics Inc, Toronto, Canada). *Red arrows* show vein graft wall. **Lower:** Velocity of vein graft blood flow.

Comprehensive hemodynamic and biomechanical assessments of the various mouse vein graft constructions have not been reported. Thus, correlation with actual human physical parameters may be limited.

Finally, imaging also remains a challenge, although an overall heightened interest in small animal imaging will probably soon provide tools to gain in vivo anatomic and biologic information in the mouse setting. For instance, commercially available high-frequency ultrasound duplex

can provide good resolution of mouse vein graft dimensions and blood velocities (Fig 5). Duplex potentially offers a technically easy, noninvasive method for longitudinal anatomic mouse vein graft imaging. However, published reports that employ vascular imaging modalities for mouse vein grafts are rare.

CONCLUSION

Despite the anatomical and physiologic differences between mice and men, and the inherent technical challenges with small animal surgery, the mouse continues to serve as an important stepping stone from laboratory bench work to bedside practice. Knowledge of key advantages and limitations of currently available mouse vein graft models will help tailor experiments to systematically unlock mechanisms that drive vein graft failure and challenge all to improve on mouse-based investigative strategies to understand vascular diseases.

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AUTHOR CONTRIBUTIONS

Conception and design: PY, BN, CO
Analysis and interpretation: PY, BN
Data collection: PY, BN, MT, CC
Writing the article: PY, BN, CO
Critical revision of the article: PY, BN, MT, CC, CO
Final approval of the article: PY, BN, MT, CC, CO
Statistical analysis: PY, MT
Obtained funding: BN, CO
Overall responsibility: CO

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