Published in final edited form as:

J Vasc Access. 2020 May ; 21(3): 328–335. doi:10.1177/1129729819874987.

An immediate access dialysis graft designed to prevent needle-related complications: Results from the initial pre-clinical studies

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Abstract

Introduction: No technology has been specifically developed with the intent to reduce needle-related vascular access injuries; a significant source of complications and abandonment. We present the initial pre-clinical study results of a novel, self-sealing, immediate cannulation dialysis graft that aims to prevent needle-related complications; to promote safe, reliable needle access; to reduce catheter use; and could facilitate home hemodialyisis.

Methods: The innovative graft design consists of two cannulation chambers with self-sealing properties and materials that prevent side and back wall needle puncture. Study and control grafts (expanded polytetrafluoroethylene) were implanted in one pig and 10 sheep in two studies over the course of 1 year. First cannulation occurred immediately post implant for all study grafts. Post-cannulation time to hemostasis, hematoma and seroma formation, infection, and patency were recorded.

Results: The two studies account for nearly 60 weeks (average 6.4 weeks/graft) of study graft follow-up. In the ovine study, average study graft time to hemostasis was 27.3 s (standard deviation = 26.3, range = 0–120), and the control averaged 177.2 s (standard deviation = 113.4, range = 60–600), $p < 0.0001$. Secondary patency was 75% and 67% for the study and control grafts, respectively. Neither study nor control groups experienced seroma, graft infections, or deaths.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.M.G. is a current employee of InnAVasc Medical, the company developing the technology reported in this manuscript. He is co-inventor of the technology, founder of the company, and owns stock in InnAVasc. He has been an employee and consultant to Humacyte, Inc., a vascular technology company, and owns stock in Humacyte. M.L. is a paid consultant for InnAVasc. C.N. is an employee of InnAVasc and owns stock in the company. D.S. has no conflicts to report. R.J.M. is a cofounder of InnAVasc and owns stock in the company. J.A.K. is an employee of InnAVasc and owns stock in the company.

Ethical approval

All animal research was performed in accordance with the National Institutes of Health Guide for Care and use of Laboratory Animals.

Discussion: All novel grafts in the studies were implanted successfully and functioned as intended. There were no complications related to tunneling of the study graft and the chamber prevented back/side wall needle injury. This novel technology may help to mitigate these needle-related complications, while allowing for early/immediate cannulation which could also reduce catheter contact time.

Keywords

Immediate access; self-sealing; needle injury; early cannulation; graft injury; catheter time; needle protection

Introduction

Since the introduction of the bridging fistula (dialysis graft) nearly a half a century ago,[1-3] there have been countless attempts to improve the technology and performance of arteriovenous grafts (AVGs) for purposes of hemodialysis (HD) access. Most technological advancements have focused on the reduction of anastomotic and outflow vein stenosis by alteration of flow dynamics or direct cellular remodeling.[4-10] To a lesser extent, companies have attempted to reduce graft clotting by altering the luminal surface of the graft and to improve upon post-dialysis bleeding, and they have made attempts to alter the graft structure and materials.[11-16]

Although the modes of failure these products aim to improve represent a sizable proportion of AVG complications, none of these technologies have been successful in significantly improving AVG usability or patency over the original, standard therapy of expanded polytetrafluoroethylene (ePTFE).[17,18] Furthermore, based on clinical experience, we hypothesize that a significant cause of many AVG complications stem from a currently unavoidable mechanism of cannulation needle-related injury (NRI), brought about by the need to puncture a dialysis graft with a large bore dialysis needle in order to access the blood for renal replacement therapy. NRI can be broken down into three main types: (1) traumatic material degradation (repetitive needle punctures), (2) graft side-wall laceration (the needle missing the lumen and slicing the side of the graft), and (3) inadvertent back wall punctures (Figure 1).

To our knowledge, there is no developed technology other than the graft described in this report, with the intent to mitigate needle-related injuries and reduce graft-related complications and abandonment associated with cannulation. Our objective in this study was to test the feasibility of implant and to assess the key enhancements of a novel vascular graft developed by our team. In this article, we present the design and pre-clinical results of a novel, self-sealing dialysis graft, designed to reduce time to hemostasis, allow for early or immediate cannulation, prevent needle-related complications and aims to promote safe, reliable needle access at every dialysis session with the potential to facilitate the transition to home HD.

Methods

The study graft combines a standard ePTFE vascular graft with a novel graft modification technology engineered with materials that provide durable, self-sealing cannulation chambers with puncture-resistant posterior and sidewall surfaces. The penetration-resistant cannulation chambers are externally molded and bonded to one contiguous segment of ePTFE and provides protection against expansion, deformation, and injury to the posterior and sidewalls of the graft by the integration of an extremely dense, yet lightweight polymer that extends along the length of the chamber to function as a needle-stopping back plate. The raised oval on the top of each chamber provides an easily identifiable cannulation zone, which when punctured in this area ensures needle access to the graft lumen. The multi-layered construction of the graft is intended to result in a self-sealing puncture zone (Figure 2). Prototype versions were numbered for tracking and each numerical change indicates an incremental update to the device design. Prototype versions 1.0 and 2.0 were used for initial bench testing and acute animal experiments and versions 3.0, 3.1, and 4.0 were used for these studies.

This research consists of two experiments to evaluate the concept and feasibility of the novel study graft. The first study consisted of a single porcine model and the second study is an ovine model including a total of 10 sheep. All surgeries and procedures were conducted with the animals under general anesthesia, in the Duke University Vivarium, under the direct supervision of the Duke Office of Animal Welfare Assurance under active IACUC protocols: A078-13-03 and A040-16-02. All animal research was performed in accordance with the National Institutes of Health Guide for Care and use of Laboratory Animals.

Although the geometric configurations differed between models, all grafts were tunneled in a standard subcutaneous fashion. Both control (Impra graft (CR Bard)) and study grafts (InnAVasc Medical, Inc., Durham, NC) were tunneled in the subcutaneous space between the vascular exposure sites using a standard graft tunneler (e.g. Kelly-Wick). To replicate conditions consistent with HD, the animals were administered intravenous heparin (40 U/kg) before each cannulation session. Cannulation of the control grafts was performed in the standard fashion by palpating the graft borders and determining the maximal impulse and/or slight thrill. Study graft cannulation was performed by clearly palpating the individual chamber and then the distinct cannulation zone as demarcated by the raised oval cannulation indicator. For both graft types, once the graft location was determined, the needle was inserted at an angle between 25° and 45° above the skin, with the bevel facing upward. At the conclusion of each study, the grafts were excised *en bloc* for gross and microscopic histologic evaluation following the scheduled final cannulations and angiogram. Basic statistics were calculated using a 2-sample independent t-test with RStudio statistical software.

Porcine study: testing of early prototypes in a porcine model (Prototype version 3.0)

The study graft and a control graft were implanted into a 50-kg female Yorkshire swine. The grafts were implanted (one on each side) from the subclavian artery to the iliac vein and tunneled in the subcutaneous space along the ventro-lateral aspect of the animal (Figure 3). Both grafts were accessed with a standard 16G HD needle immediately post implant, 12

times per access site all in one setting. This cannulation process was repeated two times per week for a total of 60 cannulations per site, to simulate approximately 5 months of regular dialysis cannulations. Post-cannulation time to hemostasis, blood loss, hematoma formation, posterior/side wall penetration, and graft patency were evaluated.

On the final cannulation day, angiography was performed through each graft immediately post cannulation to evaluate for extravasation of blood from the cannulation defects and any other technical abnormalities and then the grafts were excised.

Ovine study: testing of the study graft compared against standard-wall ePTFE (Prototype versions 3.1 and 4.0)

The study graft was tested against the proposed regulatory predicate device in a chronic sheep model. Control grafts were standard wall, non-stretch, non-heparin bound ePTFE grafts currently on the market and used for standard AVG procedures. A single-chamber prototype study graft was used for these studies due to neck length, and technical and anatomical considerations. Grafts were implanted between the carotid artery (distally) and the ipsilateral jugular vein (proximally) creating an arteriovenous shunt.

A total of 10 sheep were implanted with 14 grafts (8 study, 6 control). Four sheep were implanted with one control and one study graft on each side of the neck (with the intent to reduce the variability between study animals). Six sheep were implanted with each animal receiving only one graft unilaterally on the neck. In this cohort, two sheep were implanted with the control graft, and four sheep were implanted with the study graft. Nine sheep were survived out to 4 weeks and the 10th sheep was survived out to 20 weeks to better assess tissue incorporation over an extended period and to assess the feasibility of long-term patency in this sheep model.

At each time point, the grafts were cannulated with a standard 16G HD needle (Figure 3). The needle was left in place briefly to confirm successful placement and then removed. The study graft was cannulated immediately post implant (day 0) and at weeks 1, 2, 3, and 4. The 20-week implant was cannulated at these same time points and also at weeks 5, 6, and 8. The control graft was cannulated at the same time points as the study graft with the exception of day 0 (immediately post implantation). The experimental plan called for each graft to be cannulated four separate times at each time point for the 4-week animals and six separate times for the 20-week animal.

Angiograms were performed at 0, 2, and 4 weeks (and 20 weeks for one animal) using radiopaque contrast to document graft patency, extravasation of blood, and intra-luminal abnormalities and to determine if the graft had migrated or kinked. On the final day of the experiment (4 weeks for 9 animals, 20 weeks for 1 animal), the grafts were excised for analysis and the animals euthanized following angiography. In this study, we quantified post-cannulation time to hemostasis, hematoma formation, pseudoaneurysm development, posterior and sidewall needle penetration/injury, graft patency, and graft kinking, migration, or mal-rotation.

The safety and effectiveness of the study graft in the porcine and ovine models was compared to standard ePTFE graft by assessing the following study endpoints.

Post-cannulation time to hemostasis

Immediately following needle withdrawal, the cannulation site was blotted once with gauze and visually assessed for graft bleeding at the site. If bleeding continued, pressure was held in 30-s increments until hemostasis was achieved (time to hemostasis).

Posterior and sidewall needle penetration/injury

Posterior wall injury was noted at the time of the needle puncture procedure by tactile feedback and observation. Posterior wall penetration was apparent if the needle courses through the graft and tissue to the hub of the needle. In addition, blood did not readily back bleed from the dialysis needle tubing as the needle tip was extraluminal. This was verified on gross histologic review post explant as evidenced by hematoma formation deep to the posterior wall of the graft.

Graft patency

Graft patency was verified by angiographic imaging. For purposes of this study, graft patency was defined as continuous, antegrade blood flow through the graft with no specifically defined flow rate. Graft kinking and/or mal-rotation was documented.

Results

Porcine study

At 2 weeks, both grafts had maintained primary patency. All study graft cannulations remained intraluminal, while 100% of the needle cannulations of the control graft easily penetrated the back wall (purposeful for proof-of-concept) as confirmed by gross examination post explant. Each graft sustained 120 punctures (60 per access site—arterial zone and venous zone) over the course of the study. There was no evidence of hematoma formation from the study graft, but several large hematomas developed from the control graft (expected due to no tissue incorporation). Hemostasis was achieved in <30 s for the study graft with minimal or no pressure over the puncture site, whereas the control required digital pressure for >300 s to achieve hemostasis (Table 1). There was no evidence of extravasation of blood from the study graft as noted from conventional angiography, nor was there any indication of graft kinking at the transition zones (transition area between the cannulation chamber and the standard ePTFE regions of the graft), migration, or mal-rotation, whereas significant extravasation was observed from the needle puncture sites in the control graft (Figure 4). On gross histologic review, peri-graft hematoma was apparent around the control graft; conversely, only mild capillary injury was observed over the anterior aspect of the study graft from needle puncture sites in the skin. Overall, the study graft performance appeared to be superior to that of the control in terms of time to hemostasis, blood loss, hematoma formation, and non-back wall penetration. Overall, there were no technical difficulties encountered during implantation of the study graft.

Ovine study

The study grafts demonstrated an average time to hemostasis of 27.3 s (standard deviation (SD) = 26.3, range = 0–120), which remained stable across the study period (Figure 5), compared to the control, which averaged 177.2 s (SD = 113.4, range = 60–600), $p < 0.0001$. Data from all 10 sheep account for a total of 132 cannulations performed on the study grafts, and 86 cannulations on the control. In this study, we did not purposely counter puncture the control grafts and therefore posterior wall injury was not specifically assessed; however, all cannulations were contained within the lumen of the study graft.

Six of eight (75%) study grafts and four of six (67%) of control grafts maintained secondary patency out to 4 weeks. Grafts in the 20-week animal maintained primary patency out to 8 weeks, but were occluded at the 12-week evaluation. The animal was survived out to the full 20 weeks to evaluate histopathology. Overall, two control and four study grafts occluded once during the study and required percutaneous thrombectomy procedures. Two of the four (50%) thrombectomy procedures on the study grafts were successful in restoring patency, but thrombectomy procedures on the control grafts were unsuccessful (Table 1). All thrombectomy procedures performed on the study graft were performed through the cannulation chambers using 6 Fr and 7 Fr vascular sheaths. Minimal to no bleeding was observed following removal of the vascular sheaths from the study graft, and there was no need to place a purse string at the sheath puncture site. There was no kinking, twisting, or mal-rotation identified in any of the study or control grafts as verified by angiographic imaging and gross histological examination. In addition, there were no graft infections during the study. All study graft cannulations were contained within the lumen of the graft. Surgical procedure and implant time did not differ between placement of the control graft (141.4 min) and the study graft (142 min).

Discussion

Traumatic material degradation is a chronic process that occurs from repetitive needle punctures through the ePTFE, particularly when concentrated to a few square centimeters of material, for example, arterial cannulation zone and the venous cannulation zone in a dialysis graft.[19] As demonstrated by Charara et al.,[20] defects in ePTFE from needle punctures do not seal or close following needle removal. As such, blood and serum easily leak from these defects following needle withdrawal. In an attempt to mitigate this, it is generally recommended to allow for 2–4 weeks of “tissue ingrowth” into the ePTFE material. This tissue incorporation (scarring) facilitates in sealing the needle hole as platelets more effectively aggregate to a smaller and more elastic defect in the scar tissue itself, rather than the hole in the ePTFE.[21] However, over time, repetitive needle punctures in concentrated zones eventually leads to traumatic degradation of the base material (ePTFE) and therefore significantly reduces the integrity of the vascular conduit. This process leads to pseudoaneurysm formation and in many cases, thrombosis, bleeding, infection, pain, and ultimate graft loss.[22]

Graft side-wall laceration and inadvertent back-wall punctures are more acute type NRIs that can result in instantaneous bleeding complications such as hemorrhage or hematoma. Back-wall punctures result in bleeding from the posterior wall defect and do not allow for

application of pressure to the puncture site. Inability to apply pressure to the puncture site can result in a significant, localized hematoma, and in the acute setting, posterior wall bleeding can result in massive peri-graft bleeding and hematoma due to lack of graft incorporation. Side wall lacerations can result in more severe bleeding as the needle creates a long defect through the graft side wall (anterior to posterior), rather than a localized puncture.

Currently, the clinical literature describing cannulation problems and NRI is deficient. There are no procedural or diagnosis billing codes specific to these complications but rather broad and vague terms are used to capture dialysis access complications as a whole. Therefore, there is no clear data to elucidate the incidence of NRI based on retrospective reviews of clinically reported coding data. To date, there are no known prospective studies that have reported on the incidence of NRI and how this contributes to vascular access complications and abandonment. However, this problem is well known by most vascular access providers. Inston[23] has described the effects of cannulation on AVGs in a recent bench study with outcomes similar to previously unpublished data from our team during the development of the current study graft. Charara and Delorme have done some of the most extensive work on the effects of needle cannulation trauma on ePTFE grafts. They have observed and documented this clinically but have also been able to demonstrate this on the bench with scientific rigor.[20,21]

This report demonstrates the first attempt at mitigation of NRI in a pre-clinical model. We began with a porcine model as our team is well versed in the use of this archetype and it is a well-known model for vascular access. The porcine model is good for acute and short-term studies but has disadvantages for chronic studies due to expanded growth of the animal and a legacy of proliferative and thrombotic response following graft implantation.[24]

To investigate the long-term utility of the study graft, we felt it necessary to conduct a 20-week preclinical pilot study in a mature ovine model. Adult sheep have been utilized in vascular models previously with success, and the coagulation profile of sheep is similar to other known successful vascular models.[25,26] In addition, adult sheep (~130 lbs) have a very suitable neck length and contour to accommodate the study graft in an AV access model, and vessel size and skin qualities that replicate properties found in an adult human upper extremity.

In this report, we present data to support the proof-of-concept and feasibility of a novel dialysis graft technology designed to eliminate the risk of back and side-wall needle injuries. The results from this early study suggest that this technology promotes immediate cannulation, protection from back and sidewall needle puncture, and decreased bleeding from cannulation sites. However, it is conceivable that the construction of the cannulation chambers could potentially allow for improved durability of the cannulation zone and possibly reduces the risk of pseudoaneurysm development, infection, bleeding, and graft thrombosis. The latter potential outcomes could be the focus of future clinical studies. Although the study graft required more force to push the needle through the anterior wall of the study graft, the team observed a distinct ease of cannulation compared to the control graft due to the clear tactile feedback of the individual chamber and the raised oval

cannulation indicator. This feature improved cannulation confidence and success due to the ease of cannulation zone detection compared to the control and the resistance of luminal graft collapse upon needle contact, a stark contrast to standard ePTFE. Furthermore, obvious tactile feedback generated by the needle tip contacting the puncture-resistant back wall eliminated any question of successful cannulation.

To our knowledge, there is no dialysis access technology focusing on mitigation of the needle cannulation interface as a means of added safety and protection for patients and dialysis access providers. The features highlighted above may reduce the skill and experience required to successfully and safely cannulate the study graft. This technology could reduce the incidence of AVG complications related to NRI and could also change the AV access paradigm by providing a reliable immediate access graft, thereby reducing the need for central venous dialysis catheters and the problems with which they are associated.[27-29] Furthermore, a dialysis graft with advancements such as those described in this report could potentially facilitate the expansion of home HD programs.

Acknowledgements

We acknowledge the clinical and experimental input of Jeffrey H. Lawson, MD, PhD, in the development of this vascular access device and pre-clinical studies reported in this manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR001117, the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number R41DK108488, and the North Carolina Biotechnology Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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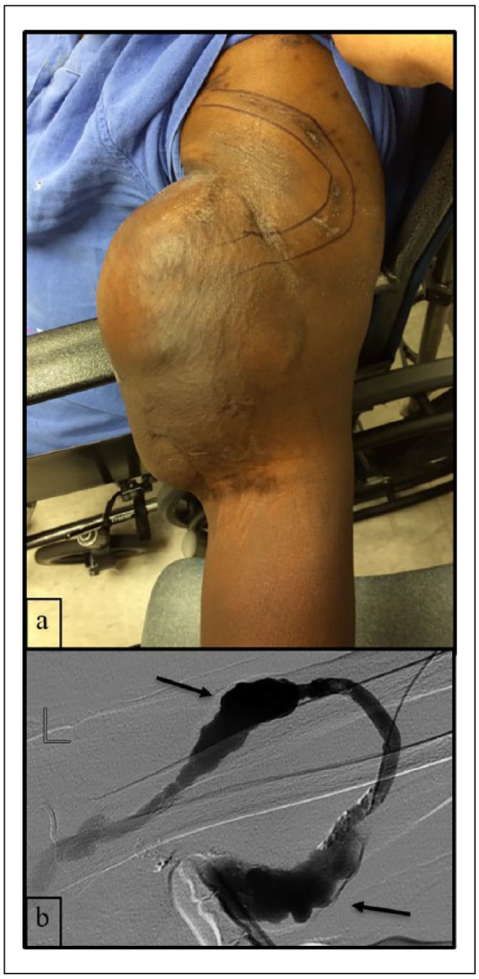

Figure 1.

(a) Massive hematoma on the left upper extremity of a hemodialysis patient secondary to an acute needle laceration injury from a graft cannulation attempt. (b) Angiography of forearm loop graft (ePTFE) with material degradation of the cannulation zones due to repetitive needle punctures. (Images courtesy of Shawn M Gage)

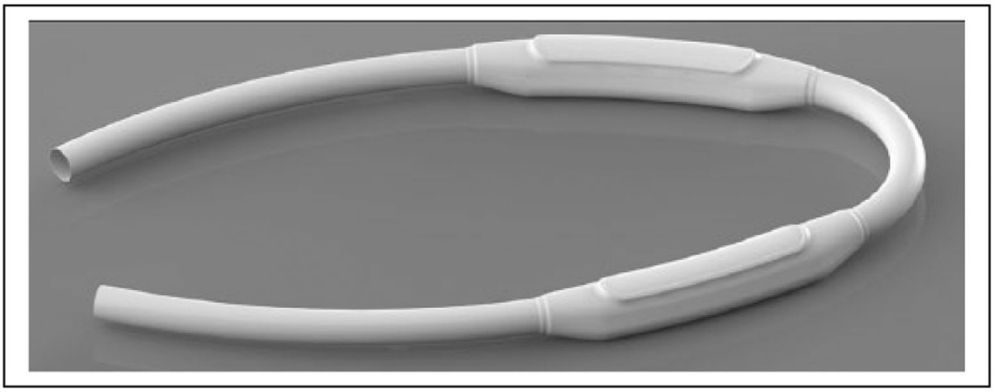

Figure 2.

Study graft (looped configuration) with two cannulation “chambers”—providing distinct arterial and venous stick zones. The chambers are designed with a raised cannulation indicator on top to denote the safe cannulation zone and a material designed to prevent needle penetration extends the length of the chamber on the posterior aspect and sidewalls. If the dialysis needle is placed in this area, it cannot penetrate through the back or side wall of the graft and the needle tip will remain in the flow lumen. Note the flattened bottom of the chamber to provide orientation and to prevent rotation in the tunnel.

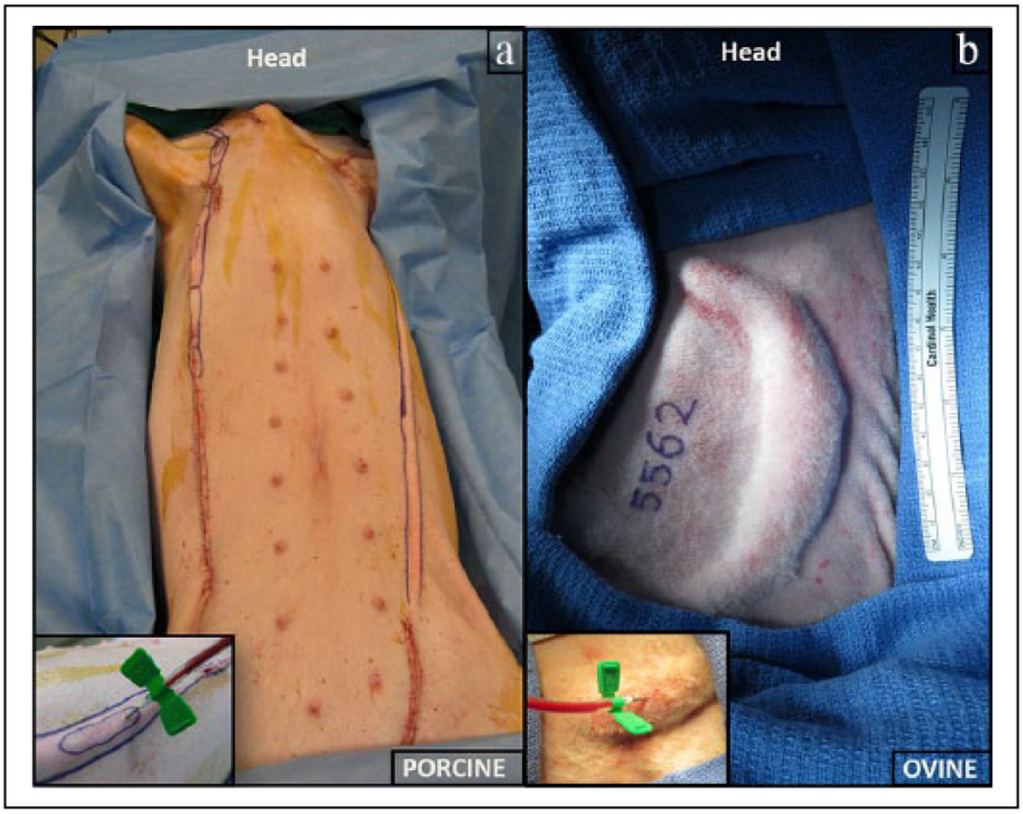

Figure 3.

Examples of the two different models used in these studies (Porcine and Ovine). We utilized the subclavian artery for inflow and the iliac vein for outflow in the porcine model (a) and the distal common carotid artery for inflow and proximal jugular vein for outflow in the ovine model (b). The insets show cannulation with a standard 16G needle on the day of implant.

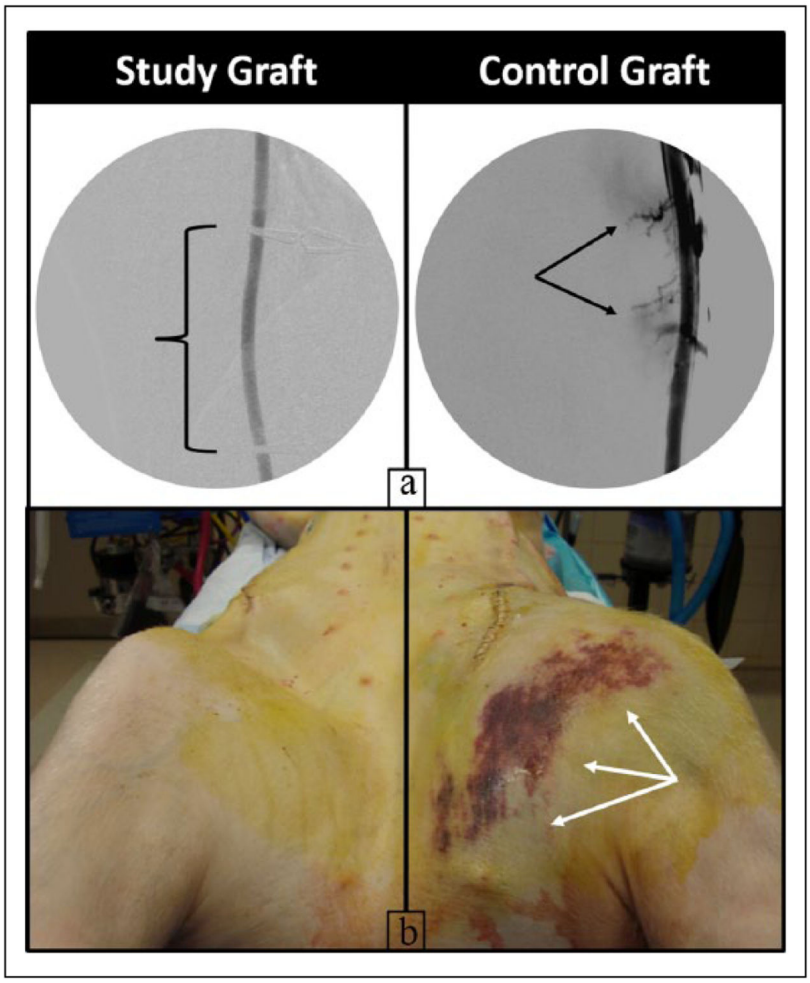

Figure 4.

Two weeks post implant. (a) Angiography of the study and control grafts immediately post cannulation (total of 60 cannulations at this time point). The bracket indicates the cannulation chamber for the study graft and the black arrows indicate extravasation of blood and contrast with the control graft. (b) Significant hematoma and ecchymosis (white arrows) on the control graft side and there is no evidence of injury on the study graft side.

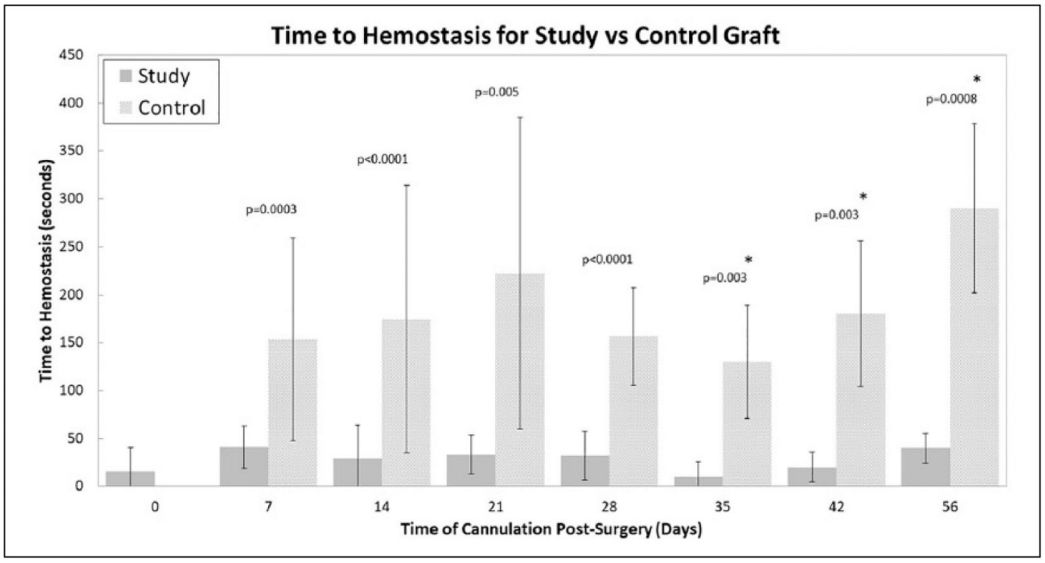

Figure 5.

Time to hemostasis analyses for ovine study. Seven of eight study grafts and five of six control grafts were cannulated out to 4 weeks. *One sheep (20-week animal) in each arm that continued cannulations out to 8 weeks. Study grafts demonstrated an average time to hemostasis of 27.3 s (SD, 26.3) [range, 0–120], compared to the control, which averaged 177.2 s (SD, 113.4) [range, 60–600], $p < 0.0001$.

Table 1.

Summary of pre-clinical study assessments and results.

	Pre-clinical Study 1: Porcine model (N = 1)		**Pre-clinical Study 2: Ovine model (N = 10)**	
	Study graft	**Control**	**Study graft**	**Control**
Total grafts (n)	1	1	8	6
Posterior/sidewall needle penetration (%)	0	100[a]	0	Not assessed
Hematoma formation at puncture site	None	Several large hematomas	None	Minor
Total cannulations per graft (n)	120 (60 per chamber)	120 (60 per access site)	16.5	14.3
Total cannulations per study arm (n)	120	120	132	86
Post cannulation time to hemostasis; mean (SD) [range]	<30 s	>300 s	27.3 s (26.3) [0–120]	177.2 s (113.4) [60–600]
Extravasation of blood/contrast on angiogram	None	Significant	–	–
Graft kinking, migration, or mal-rotation	None	None	None	None
Graft patency at conclusion of study period (secondary) (%)	1/1	1/1	6/8 20-week model lost patency after week 8 assessment	4/6 20-week model lost patency after week 8 assessment
Graft infection	None	None	None	None
Implantation time	–	–	142 min	141.4 min
Histology	Evidence of minor anterior bleeding/capillary injury No posterior wall injury	Significant hematoma from posterior wall and obvious needle defects	Standard ePTFE tissue healing/ scarring response and fibroblast deposition	Standard ePTFE tissue healing/ scarring response and fibroblast deposition

SD: standard deviation

ePTFE: expanded polytetrafluoroethylene.

[a]Purposeful for proof of concept.