Translational rat model of arteriovenous fistula for the study of the pathophysiology and molecular imaging of dialysis access stenosis and development of endovascular therapies

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Learning objectives

1. Introduce a catheterizable rat vascular model for the translational study of arteriovenous fistula (AVF)

2. Understand advantages of the model for developing imaging techniques and therapies regarding vascular remodeling and AVF stenosis.

Background

End stage renal disease is a pressing healthcare issue in the United States with over 800,000 patients currently being treated at an annual expense of $42 billion [1]. About 82% of patients receive hemodialysis through an arteriovenous graft (AVG) or fistula (AVF) for which patency is fundamental for effective dialysis [2]. AVF dysfunction results from vascular remodeling (VR) characterized by neointimal hyperplasia (NH) [3]. Progressive NH culminates in stenosis leading to increased resistance, decreased flow and thrombosis [4].

Current imaging methods, like fistulography, only detect late morphological sequelae of VR (Fig. 1). In contrast, near-infrared fluorescence (NIRF) optical imaging can detect molecular alterations initiating VR, which precede the anatomical changes. NIRF imaging has been previously demonstrated in vascular models as has endovascular NIRF imaging of protease activity [5,6]. Molecular mediators, such as matrix-metalloproteases, play key roles in NH and subsequent VR, and have been shown to be upregulated in stenotic AVFs [4,7,8]. Creation of a catheterizable AVF model would facilitate further development of imaging techniques and endovascular therapies targeting early VR.

Images for this section:
Fig. 1: Typical findings at fistulography in a patient with an arteriovenous fistula and failed dialysis session. The patient was sent to interventional radiology for further evaluation and treatment. Initial diagnostic fistulogram (left) demonstrates a stenosis (arrow) as the cause of the poor flow and failed dialysis attempt. Following angioplasty (right) the vessel is now fully patent.
Findings and procedure details

AVF Creation:

Following administration of anesthesia, an oblique incision was made in the groin of 10wk old Sprague-Dawley rats. The common femoral artery and vein (CFA, CFV) were isolated (Fig. 2). Following proximal and distal vessel clamping, the CFA was ligated at its distal aspect. A venotomy was made on the ventral surface of the CFV, and an end-to-side anastomosis was created using interrupted 10-0 suture (Fig. 3). The vessel clamps were then removed and anastomotic leaks were ruled out (Fig 4.) Initial patency of the AVF was visually assessed by confirming filling and pulsatility of the CFV. Finally the soft tissues were closed with 5-0 suture.

AVF Imaging:

Six weeks following AVF creation, color and spectral Doppler ultrasound imaging were performed on the surgical site to assess for AVF patency (Fig. 5). Additionally, in order to demonstrate feasibility of accessing the common femoral AVF for potential catheter directed interventions or therapies, the rats were catheterized and angiography was performed. A paramidline incision was made over the left neck. The left common carotid artery (LCCA) was isolated (Fig. 6). Proximal and distal vessel clamps were applied. An arteriotomy was made with a 24G Angiocath needle. Next, 8-0 suture was passed through the inferior lip of the arteriotomy and lifted to assist passage of a 1.5F catheter into the LCCA as the proximal clamp was removed. Under fluoroscopy, the catheter was advanced down the aorta and into the common iliac artery. Intravenous contrast (2mL) was injected to again assess patency of the AVF (Fig. 7). The catheter was then removed and the LCCA arteriotomy was closed with 8-0 suture. The soft tissues were then closed with 5-0 suture. Repeat studies were performed in similar fashion as the LCCA remained patent despite multiple catheterizations (Fig. 6). In vivo surgical assessment (Fig. 8) and magnified views using a microscope of AVF explants (Fig. 9) confirmed angiographic findings. Histology demonstrated neointimal hyperplasia in the vein next to the anastomosis (Fig. 10) and in the dilated proximal (central) vein (Fig. 11), with normal control vein from the contralateral side for comparison (Fig. 12).

Results:

In this initial technical feasibility study, 7/9 (78%) attempted AVFs were patent six weeks after creation as assessed with angiography via a LCCA approach.

Future Directions:
Using this translational vascular model for evaluation of the development of flow limiting stenosis in hemodialysis access, future experiments include using NIRF optical imaging to further evaluate the early pathogenesis of neointimal hyperplasia and vascular remodeling. Once the important modulating factors are identified, we plan to pursue development of catheter directed therapies and endovascular imaging techniques for the early diagnosis and potential prevention of hemodialysis access malfunction.

Images for this section:

![Image of femoral artery and vein](image_url)

**Fig. 2:** The common femoral artery and vein are isolated for creation of an arteriovenous fistula.
**Fig. 3:** View of an arteriovenous fistula at surgery. The common femoral artery and vein are clamped centrally; the common femoral vein is also clamped peripherally. The common femoral artery peripheral to the anastomosis has been tied off with suture (outside field of view). The anastomosis is an end-to-side artery-to-vein technique. The suture needle is seen during an interrupted stitch of the anastomosis.
Fig. 4: The arteriovenous fistula (same AVF as in Fig. 3) is again seen after removal of the clamps and completion of the anastomosis. In this particular view, the artery courses over top of the vein prior to insertion at the end-to-side anastomosis. Prior to closure, no bleeding from the anastomosis is confirmed. Furthermore initial patency is checked for filling and pulsatility in the vein. At the time of this picture, there was vasospasm and venous filling is less apparent. However, after a few minutes of waiting and application of a few drops of nitroglycerine (100 mcg/ml) onto the vessels, pulsatile blood flow was confirmed. The tied-off artery peripheral to the anastomosis is also seen (white arrow).
Fig. 5: Ultrasound confirmation of an AVF with color and spectral Doppler imaging. At the fistula site, color Doppler ultrasound demonstrates aliasing from turbulent flow (A). Spectral Doppler ultrasound (B) demonstrates mixed arterial and venous waveforms (C).
Fig. 6: Isolation of the left common carotid artery for insertion of a catheter. Note remnant suture in the artery from prior closure of an arteriotomy from a previous catheterization (arrow), demonstrating feasibility of repeated catheterizations for potential imaging and treatment at multiple time points.
Fig. 7: Angiographic evaluation of the arteriovenous fistula. There is a stenosis just central to the anastomosis from vascular remodeling. The common femoral vein has otherwise dilated over time from arterial flow. Note the catheter artifact in close proximity to the fistula suggesting this model could potentially allow for catheter directed therapy and endovascular imaging.
Fig. 8: Surgical inspection of an arteriovenous fistula six weeks after creation with visual assessment of patency. The common femoral vein has dilated in caliber secondary to the high pressure arterial flow over time, suggesting a patent fistula.
Fig. 9: Magnified view of the explanted arteriovenous fistula. An area of approximately 50% stenosis is again seen just central to the anastomosis, which corresponds to the findings on the angiographic fistulogram. The blue color in the tissue is an artifact of the microscope's filter.
Fig. 10: Histology with H&E stain (40X magnification) at the level of the arteriovenous fistula demonstrates cross-sectional views of the immediately adjacent artery (A) and vein (V). Neointimal hyperplasia has developed in the vein segment extending approximately from the 1 o'clock to 6 o'clock positions (black arrows).
Fig. 11: Histology with H&E stain (40X magnification) of the vein proximal (central) to the anastomosis. The vein has dilated in caliber and there is neointimal hyperplasia extending approximately from the 12 o'clock to 7 o'clock positions (black arrows).
Fig. 12: Histology with H&E stain (40X magnification) of the contralateral femoral vein for control comparison. There is no evidence of vascular remodeling.
Conclusion

1. Creation of a catheterizable rat model of AVF is feasible

2. AVFs can be imaged multiple times using the same technique.

3. The model allows angiographic assessment of AVF morphology to correlate with gross and histologic findings.

4. The approach permits whole animal and intravascular optical imaging based on endovascular delivery of probes targeting biomarkers of VR.

5. The technique allows for targeted endovascular therapies to treat early VR.

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