

# Ted R. Kohler, M.D.



- ENDOVASCULAR THERAPY
- EFFECT OF BLOOD FLOW ON INTIMAL HYPERPLASIA AND ACCESS GRAFT FAILURE
- DIALYSIS ACCESS GRAFTS

## FUNDING

National Institutes of Health  
Northwest Kidney Foundation

### Endovascular Therapy

**E**ndovascular therapy is an exciting new approach to aneurysm repair that uses a catheter-based delivery system rather than conventional open techniques. Patient morbidity and hospital stay are dramatically decreased. Endovascular grafts are held open and in proper position by attached metallic stents and are placed by a simple arterial cutdown or, in some cases, percutaneously. These devices have been very successful in early clinical trials and are soon to be approved for market release by the FDA. It remains to be seen, however, if these devices will perform as well

### Effect of Blood Flow on Intimal Hyperplasia and Access Graft Failure

Vascular surgery has made tremendous advances in the last few decades. Bypass grafts, angioplasty, and stents are now standard treatment for arterial insufficiency and aneurysm disease in peripheral arteries. However, long-term success of these procedures is limited by a process of wound healing called intimal hyperplasia, in which wall thickening from smooth muscle cell proliferation narrows the lumen.

Intimal hyperplasia causes failure of almost one-third of all vascular reconstructions. Much research has been devoted to understanding the cellular pathology of

---

*Erythropoietin, normally made by the kidney, stimulates production of red blood cells. Patients with renal failure do not make enough of this hormone and as a result are anemic.*

---

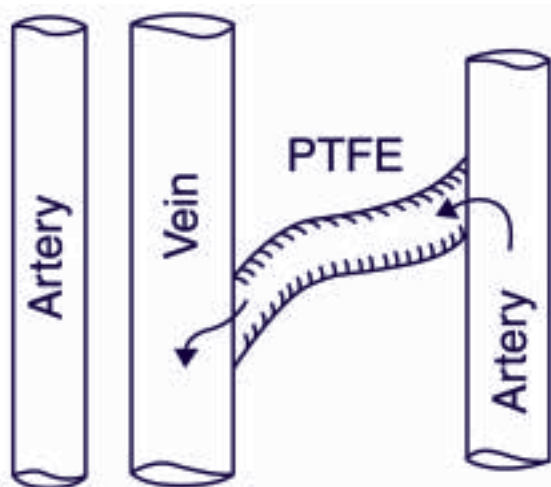
over the long term (decades) as conventional grafts. The primary concern is whether or not the devices will remain well attached to the native artery at either end despite the native vessel's tendency to dilate over time.

Dr. Kohler and Dr. David Glickerman, from interventional radiology, began the endovascular therapy program at the Seattle VA hospital. We are one of several centers in the country participating in an FDA-sponsored trial of the AneuRx endovascular graft. Dr. Kohler was on the planning committee for the VA Cooperative Trial of Open versus Endovascular Repair of abdominal aortic aneurysms. This trial will begin in October, 2002 at the Seattle VA.

this process and to developing ways to combat it with drugs, new devices, and genetic modification of the cells involved. Our laboratory is studying the effects of altered blood flow on intimal hyperplasia, and is evaluating new vascular devices to reduce restenosis.

### Dialysis Access Grafts

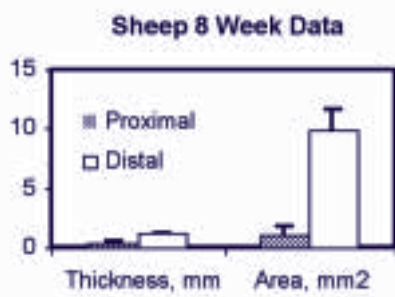
Effective renal dialysis requires several hundred cc's per minute of blood flow. To accomplish this, a fistula is created between an artery and vein, typically in the arm. This provides a high-flow conduit just under the skin surface where it can be accessed by needle puncture. Unfortunately, these fistulae have a high failure rate,



**FIGURE 1:** Fistula created between artery and vein to provide high-flow conduit

even higher than other vascular grafts. Re-operation for failed access is a major cause of morbidity, prolonged hospital stay, and increased cost in the treatment of renal failure. Most access failures are caused by intimal hyperplasia at the venous end of the graft. This is very surprising since in animal models we have found that increased blood flow reduces wall thickening after placement of prosthetic arterial grafts.

We are studying this problem in an animal model. Polytetrafluoroethylene (PTFE) grafts like those used in humans are placed in the neck of sheep, and measurements are made of the narrowing at the junction of the graft and native vessels. We have found that standard grafts fail within two to three months due to narrowing, which is much more pronounced at the venous end (see graph). Active thrombosis along the graft surface, particularly at the venous end, appears to be a major contributing factor. Thickening is greatly reduced if the grafts are sewn into an artery instead of a vein, even if blood flow is increased by creation of an artery-to-vein



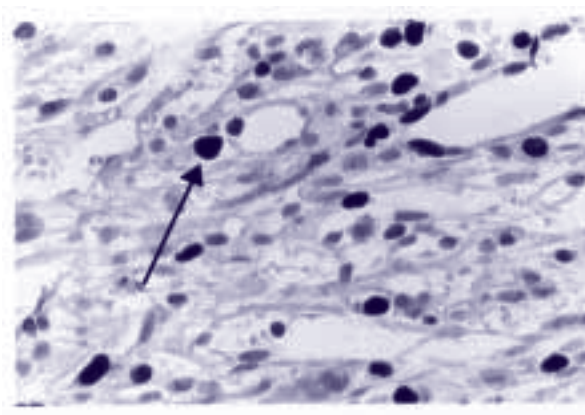
**GRAPH 1:** Sheep Eight Week Data

fistula beyond the graft. We have also found that special coating of the graft surface with phospholipids can stop this thickening process.

The three principle components of graft healing and lumen narrowing are endothelial ingrowth, smooth muscle cell proliferation, and thrombosis. These are evaluated using scanning electron microscopy, morphometry, and immunohistochemistry. We can also use simulated dialysis to assess the potential role in graft failure of the various components of the dialysis procedure.

Like the clinical specimens, the sheep lesions have focal regions of prominent cellular proliferation, often adjacent to thrombus and in granulation tissue surrounding the graft. This can be seen in Figure 2, showing a proliferating-cell-nuclear-protein (PCNA)-positive nucleus marked by an arrow.

Organizing thrombus contributes significantly to luminal narrowing. The continued presence of thrombus and high rates of cellular proliferation suggest ongoing injury as an important cause of lesion formation. Rapid development of lesions morphologically similar to lesions makes this model uniquely suited for study of the cellular mechanisms of dialysis failure.



**FIGURE 2:** PCNA-positive nucleus

We have determined that tissue factor (a stimulant of thrombosis) is increased along the length of the access graft, at both early and late times, possibly in response to this injury (Table 1). Elevated levels of this clotting factor may explain the thrombosis we have observed. Studies are underway to determine the cellular source of this enzyme and whether local drug infusion can block its production and therefore the development of intimal hyperplasia.

We will compare standard PTFE grafts with grafts that are more porous. Increased porosity allows in-growth of capillaries across the graft to the lumen, where they spread and form an endothelial lining that may protect against thrombosis and intimal hyperplasia. We are also using this model to study the use of arterial grafts to deliver gene therapy.

PTFE grafts are seeded with smooth muscle cells that have been transduced with the erythropoietin (epo) gene (Dr. William Osborne, PI). Erythropoietin, normally made by the kidney, stimulates production of red blood cells. Patients with renal failure do not make enough of this hormone and as a result are anemic. We will use a uremic sheep model to find out if epo made by cells placed in dialysis access grafts can reverse the anemia of chronic renal failure.

LOCATION	TISSUE FACTOR ACTIVITY (+/-SD)	TISSUE FACTOR PROTEIN	FIBRIN
Normal Artery	22.0 +/- 18.0	-	-
Graft near Artery	113.5 +/- 10.9 *	++	+
Graft near Vein	194.5 +/- 15.2 *	+++	+
Normal Vein	32.0 +/- 1.5	-	-

(N=4. \*=p<.05, one-tailed Mann-Whitney comparison)

TABLE 1: Tissue Factor Levels in Sheep Access Grafts

RELATED PUBLICATIONS

1. Mattsson, E., Kohler TR, Vergel S, Liao JK, Clowes AW. Increased Blood Flow Induces Regression of Intimal Hyperplasia. *Arterio Thromb Vasc Biol*, 1997; 17:2245-2249.
2. Kohler, TR, Kirkman, TR. Central venous catheter failure is induced by injury and can be prevented by stabilizing the catheter tip. *J Vasc Surg*, 1998; 28:59-66.
3. Kohler, TR, Kirkman, TR. Dialysis access failure: A sheep model of rapid stenosis. *J Vasc Surg*, 1999; 30:744-51.
4. Gibson KD, Caps MT, Kohler TR, Hatsukami TS, Gillen DL, Aldassy M, Sherrard DJ, Stehman-Brenn CO. Assessment of a Policy to Reduce Placement of Prosthetic Hemodialysis Access. *Kid Int*, 2001; 59:2335-45.
5. Fontaine AB, Nicholls S, Borsa JJ, Hoffer E, Bloch RD, Kohler TR. Seat Belt Aorta: Endovascular Management with a Stent-Graft. *J Endovasc Ther*, 2001; 8:83-86.
6. Leotta DF, Paun M, Beach KW, Kohler TR, Zierler RE, Strandness DE Jr. Measurement of Abdominal Aortic Aneurysms using Three-Dimensional Ultrasound Imaging: Preliminary Report. *J Vasc Surg*, 2001; 33:700-7.
7. Gibson KD, Stehman-Brenn CO, Kohler TR. Use of the vascular diagnostic laboratory in improving the success of angioaccess procedures. *Sem Vasc Surg*, 2001; 14:222-26.
8. Gibson KD, Gillen DL, Caps MT, Kohler TR, Sherrard DJ, Stehman-Breen CO. Vascular access and incidence of revisions: A comparison of prosthetic grafts, simple autogenous and venous transposition fistulas from the United States Renal Data System Dialysis Morbidity and Mortality Study (USRDS DMMS). *J Vasc Surg*, 2001; 34:694-700.
9. Yutan E, Glickerman DJ, Caps MT, Hatsukami T, Harley JD, Kohler TR, Davies MG. Percutaneous transluminal revascularization for renal artery stenosis: VA Puget Sound Health Care experience. *J Vasc Surg*, 2001; 34:685-93.
10. Leotta DF, Paun M, Beach KW, Kohler TR, Zierler RE, Strandness DE Jr. Measurement of Abdominal Aortic Aneurysms using Three-Dimensional Ultrasound Imaging: Preliminary Report. *J Vasc Surg*, 2001; 33:700-7.

DEPARTMENT CO-INVESTIGATORS

Alexander W. Clowes, M.D. / David Hasenstab, Ph.D.

OTHER CO-INVESTIGATORS

David Glickerman, M.D.; UW Department of Radiology / Steve Hanson, M.D.; Emory University / Tom R. Kirkman; BioDevelopment Associates, LLC / William Osborne, Ph.D.; UW Department of Pediatrics