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Original Investigation

# Correlation of Pre-existing Vascular Pathology With Arteriovenous Graft Outcomes in Hemodialysis Patients

*Michael Allon, MD,[1] Silvio Litovsky, MD,[2] Carlton J. Young, MD,[3] Mark H. Deierhoi, MD,[3] Jeremy Goodman, MD,[3] Michael Hanaway, MD,[3] Mark E. Lockhart, MD, MPH,[4] and Michelle L. Robbin, MD[4]*

**Background:** Arteriovenous grafts (AVGs) are prone to neointimal hyperplasia leading to AVG failure. We hypothesized that pre-existing pathologic abnormalities of the vessels used to create AVGs (including venous intimal hyperplasia, arterial intimal hyperplasia, arterial medial fibrosis, and arterial calcification) are associated with inferior AVG survival.

**Study Design:** Prospective observational study.

**Setting & Participants:** Patients with chronic kidney disease undergoing placement of a new AVG at a large medical center who had vascular specimens obtained at the time of surgery (n = 76).

**Predictor:** Maximal intimal thickness of the arterial and venous intima, arterial medial fibrosis, and arterial medial calcification.

**Outcome & Measurements:** Unassisted primary AVG survival (time to first intervention) and frequency of AVG interventions.

**Results:** 55 patients (72%) underwent interventions and 148 graft interventions occurred during 89.9 years of follow-up (1.65 interventions per graft-year). Unassisted primary AVG survival was not associated significantly with arterial intimal thickness (HR, 0.72; 95% CI, 0.40-1.27; $P = 0.3$), venous intimal thickness (HR, 0.64; 95% CI, 0.37-1.10; $P = 0.1$), severe arterial medial fibrosis (HR, 0.58; 95% CI, 0.32-1.06; $P = 0.6$), or severe arterial calcification (HR, 0.68; 95% CI, 0.37-1.31; $P = 0.3$). The frequency of AVG interventions per year was associated inversely with arterial intimal thickness (relative risk [RR], 1.99; 95% CI, 1.16-3.42; $P < 0.001$ for thickness $<10$ vs $>25$ $\mu$m), venous intimal thickness (RR, 2.11; 95% CI, 1.39-3.20; $P < 0.001$ for thickness $<5$ vs $>10$ $\mu$m), arterial medial fibrosis (RR, 3.17; 95% CI, 1.96-5.13; $P < 0.001$ for fibrosis $<70\%$ vs $\geq 70\%$), and arterial calcification (RR, 2.12; 95% CI, 1.31-3.43; $P = 0.001$ for $<10\%$ vs $\geq 10\%$ calcification).

**Limitations:** Single-center study. Study may be underpowered to demonstrate differences in unassisted primary AVG survival.

**Conclusions:** Pre-existing vascular pathologic abnormalities in patients with chronic kidney disease may not be associated significantly with unassisted primary AVG survival. However, vascular intimal hyperplasia, arterial medial fibrosis, and arterial calcification may be associated with a decreased frequency of AVG interventions.

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***INDEX WORDS:*** Arteriovenous graft; intimal hyperplasia; vascular calcification; medial fibrosis.

Although the use of arteriovenous fistulas (AVFs) for vascular access in the United States has increased substantially during the past few years, ~25% of hemodialysis patients continue to use arteriovenous grafts (AVGs).[1] The major disadvantages of AVGs are their relatively short cumulative survival (median of ~2 years) and frequent stenosis and thrombosis, requiring salvage procedures to uphold their patency for dialysis.[2] Previous research has not identified specific demographic or clinical features associated with AVG survival.[3] Both experimental models and studies of humans have implicated neointimal hyperplasia at the graft-vein or graft-artery anastomosis in the pathogenesis of AVG stenosis.[4,5] This observation raises the possibility that pathologic abnormalities present in the native artery or vein to which an AVG is anastomosed may predispose the patient to accelerated neointimal hyperplasia and thereby lead to early AVG failure. Specifically, pre-existing arterial or venous intimal hyperplasia may predispose to accelerated neointimal hyperplasia after vascular access creation. Likewise, arteries with substantial medial fibrosis or calcification may be stiff and thus produce excessive shear stress after vascular access creation, thereby promoting the development of neointimal hyperplasia and subsequent AVG failure.

A limited number of studies have evaluated pre-existing arterial abnormalities in patients with chronic kidney disease (CKD). These studies showed arterial

*From the [1]Division of Nephrology, [2]Department of Pathology, [3]Division of Transplant Surgery, and [4]Department of Radiology, University of Alabama at Birmingham, Birmingham, AL.*

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*Address correspondence to Michael Allon, MD, Division of Nephrology, PB, Rm 226, 1530 Third Ave S, Birmingham, AL 35294. E-mail: mdallon@uab.edu*



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medial fibrosis, calcification, and intimal hyperplasia.[6,7] Pre-existing arterial intimal hyperplasia was associated with decreased AVF survival in one report,[7] whereas arterial medial fibrosis was not associated with AVF nonmaturation in another study.[6] There are contradictory published data about the presence of intimal hyperplasia in the native veins of patients with CKD, with some investigators describing frequent and severe intimal hyperplasia[8,9] and others not observing it.[6] To our knowledge, there are no published data for whether pre-existing vascular abnormalities in patients with CKD are associated with AVG outcomes. The goal of our pilot study was to quantify pre-existing arterial and venous intimal thickness, arterial medial fibrosis, and arterial calcification in the vessels used to create an AVG and evaluate whether these pathologic abnormalities are associated with unassisted primary AVG survival. As a secondary end point, we evaluated the association between these vascular abnormalities and the frequency of interventions required to maintain AVG patency for dialysis.

## METHODS

### Overview of Study Design

We invited patients with CKD who were scheduled for creation of a new AVG to participate in this prospective observational study, which had received approval from our local institutional review board. Patient recruitment occurred between September 1, 2008, and April 30, 2011, with follow-up through September 30, 2012. The surgeon determined the optimal location of the AVG after clinical evaluation and review of preoperative ultrasound vascular mapping. During AVG creation, the surgeon obtained small specimens of the artery and vein used to perform the vascular anastomoses. A pathologist without knowledge of the patient's clinical information assessed histologic abnormalities in the vascular specimens. AVGs typically were cannulated for dialysis 2-3 weeks after creation. AVG survival was determined prospectively. Finally, we evaluated the association of frequency of AVG interventions with the patient's pre-existing vascular pathology.

### Study Population

Approximately 500 hemodialysis patients receive their medical care under the supervision of clinical nephrologists at the University of Alabama at Birmingham. Almost all patients have their hospitalizations and surgical and radiologic access procedures at University of Alabama at Birmingham Hospital, improving the quality and completeness of follow-up information for vascular access procedures and outcomes. The electronic medical record was used to extract demographic and clinical information for the study patients. Two full-time vascular access coordinators employed by the Division of Nephrology maintained a prospective computerized database of all access procedures and complications.[10]

### Preoperative Vascular Mapping

Each patient underwent preoperative ultrasound vascular mapping to assess the diameter of the vessels and exclude the presence of stenosis or thrombosis in the draining vein. AVFs were placed preferentially in patients with suitable vascular anatomy. AVGs were created in patients with anatomy unsuitable for AVF creation or those thought to be at high risk of AVF nonmaturation. Minimum sonographic criteria for AVG creation were arterial diameter of 2 mm, venous diameter of 4 mm, and the absence of stenosis or thrombosis in the draining vein.[11] AVGs were placed preferentially in the upper extremity. However, in patients who had exhausted the vasculature of both upper extremities, the AVG was created in the thigh (provided that the patient did not have significant peripheral vascular disease).

### Surgical Procedure

Four experienced surgeons created all the AVGs at a single hospital. Of 83 study patients, 72 (87%) had already initiated dialysis therapy prior to creation of the AVG and were dialyzing with a tunneled dialysis catheter. The polytetrafluoroethylene AVG was placed at 1 of 3 anatomic locations, forearm, upper arm, or thigh, on the basis of clinical evaluation and the preoperative vascular mapping. The surgeon used an end-to-side anastomosis between the AVG and vein and an end-to-side anastomosis between the AVG and artery. At the time of AVG creation, the surgeon obtained partial (elliptical) specimens (~5 mm in length) of the artery and vein from the sites used for the anastomoses. The surgeon was able to obtain the vascular samples without compromising the technical outcome of the surgery in >90% of AVG procedures.

### Pathologic Studies of the Vascular Specimens

The arterial and venous specimens obtained at the time of AVG surgery were fixed in 10% formalin and processed for light microscopy. A single pathologist (S.L.) who had no knowledge of the patient's clinical information or AVG outcome evaluated all tissue samples. Hematoxylin and eosin stains were used to assess the maximal thickness of the arterial and venous intima (measured between the endothelium and internal elastic lamina), trichrome

**Table 1.** Clinical Characteristics of Study Patients

| Characteristic | Value |
|---|---|
| Age ≥ 55 y | 47 (57) |
| Female sex | 52 (63) |
| Black race | 70 (84) |
| Comorbid condition | |
| Diabetes | 49 (59) |
| HTN | 79 (95) |
| CAD | 19 (23) |
| PVD | 7 (8) |
| CVD | 14 (17) |
| CHF | 15 (18) |
| Thigh graft | 30 (36) |
| Antiplatelet agent | 45 (54) |
| Aspirin | 43 (52) |
| Clopidogrel | 7 (8) |
| Statin | 44 (53) |
| ACEi/ARB | 52 (63) |
| CCB | 34 (41) |

*Note:* Values are given as number (percentage).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CVD, cerebrovascular disease; HTN, hypertension; PVD, peripheral vascular disease.