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# Medial Fibrosis, Vascular Calcification, Intimal Hyperplasia, and Arteriovenous Fistula Maturation

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**Background:** Arteriovenous fistulas (AVFs) for hemodialysis frequently fail to mature because of inadequate dilation or early stenosis. The pathogenesis of AVF nonmaturation may be related to pre-existing vascular pathologic states: medial fibrosis or microcalcification may limit arterial dilation, and intimal hyperplasia may cause stenosis.

**Study Design:** Observational study.

**Setting & Participants:** Patients with chronic kidney disease (N = 50) undergoing AVF placement.

**Predictors:** Medial fibrosis, microcalcification, and intimal hyperplasia in arteries and veins obtained during AVF creation.

**Outcome & Measurements:** AVF nonmaturation.

**Results:** AVF nonmaturation occurred in 38% of patients despite attempted salvage procedures. Preoperative arterial diameter was associated with upper-arm AVF maturation ($P = 0.007$). Medial fibrosis was similar in patients with nonmaturing and mature AVFs (60% ± 14% vs 66% ± 13%; $P = 0.2$). AVF nonmaturation was not associated with patient age or diabetes, although both variables were associated significantly with severe medial fibrosis. Conversely, AVF nonmaturation was higher in women than men despite similar medial fibrosis in both sexes. Arterial microcalcification (assessed semiquantitatively) tended to be associated with AVF nonmaturation (1.3 ± 0.8 vs 0.9 ± 0.8; $P = 0.08$). None of the arteries or veins obtained at AVF creation had intimal hyperplasia. However, repeated venous samples obtained in 6 patients during surgical revision of an immature AVF showed venous neointimal hyperplasia.

**Limitations:** Single-center study.

**Conclusion:** Medial fibrosis and microcalcification are frequent in arteries used to create AVFs, but do not explain AVF nonmaturation. Unlike previous studies, intimal hyperplasia was not present at baseline, but developed de novo in nonmaturing AVFs.

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***INDEX WORDS:*** Arteriovenous fistula; arteriovenous access; dialysis access.

A reliable vascular access is critical for delivery of adequate hemodialysis in patients with end-stage renal disease. The National Kidney Foundation's KDOQI (Kidney Disease Outcomes Quality Initiative) vascular access guidelines, most recently updated in 2006, strongly recommend maximizing arteriovenous fistula (AVF) use in all patients with suitable vascular anatomy.[1] Achieving this goal entails a number of intermediate steps, including pre–end-stage renal disease care by a nephrologist, pre–end-stage renal disease access surgery, adequate AVF maturation, and successful AVF cannulation by the dialysis staff.[2] An unanticipated byproduct of aggressive AVF placement is the high proportion of AVFs that fail to mature, that is, are not suitable for dialysis. Whereas 25-30 years ago, only ~10% of new AVFs failed to mature,[3-5] in subsequent years, this proportion has increased to 20%-50%.[2] In a recent multicenter randomized clinical trial of 877 participants, AVF nonmaturation occurred in 60% of patients.[6] Thus, AVF nonmaturation has emerged as the major obstacle to increasing AVF use in dialysis patients.

Better understanding of the pathogenesis of AVF nonmaturation is imperative to achieve the KDOQI AVF goals.[7] AVFs are created using direct anastomosis between a native artery and vein. Sonographic preoperative vascular mapping is widely promoted to identify vessels suitable for AVF creation by setting minimum vascular diameters and ensuring vessel patency.[2] Although preoperative mapping increases AVF placement, it does not decrease AVF nonmaturation.[6,8-11] This disappointing outcome suggests the existence of additional vascular properties affecting

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AVF immaturity that are not measured using standard preoperative ultrasound mapping.

After creation of a successful AVF, arterial blood flow increases 10- to 20-fold.[7] This increase in blood flow is associated with arterial and venous dilation. Progress in elucidating AVF nonmaturation has been hampered by our lack of understanding of intrinsic vascular abnormalities that impair vascular dilation. A plausible hypothesis is that pre-existing abnormalities in the artery or vein used to create an AVF may impede AVF maturation. Specifically, medial fibrosis or microcalcification may limit arterial dilation,[12] and intimal hyperplasia may cause stenosis.[13] However, there is limited published evidence to address these hypotheses. A pilot study from Korea described the frequent occurrence of intimal hyperplasia in arteries used to create AVFs, and the presence of intimal hyperplasia was associated with decreased AVF survival.[14] Two small studies reported frequent intimal hyperplasia in veins used for AVF creation, but did not correlate this pathologic finding with AVF maturation.[15,16]

The goal of the present study was to evaluate the potential impact of pre-existing vascular abnormalities on AVF outcomes. Specifically, we postulated that pre-existing medial fibrosis, microcalcification, and intimal hyperplasia are predictive of AVF nonmaturation. To test these hypotheses, we obtained arterial and venous specimens from patients with chronic kidney disease (CKD) undergoing AVF surgery and correlated pathologic abnormalities with AVF outcomes. Additionally, in a subset of patients undergoing subsequent surgical revision of a nonmaturing AVF, vein specimens were obtained and compared with those obtained at initial AVF creation.

## METHODS

### Overview of Study Design

Patients with CKD scheduled for creation of a new AVF were invited to participate in this prospective observational study, which had been approved by our local institutional review board. Preoperative duplex ultrasonography was performed to measure arterial and venous diameters and exclude stenosis or thrombosis in the draining veins. At the time of AVF creation, the surgeon obtained specimens of the artery and vein. A pathologist who was unaware of patients' clinical information assessed the specimens for arterial medial fibrosis and microcalcification and arterial or venous intimal hyperplasia. AVF suitability for dialysis within 6 months of AVF creation was determined clinically. Finally, we determined the predictive value of arterial medial fibrosis and microcalcification for AVF nonmaturation in our patient population. In a subset of patients who underwent surgical revision of the anastomosis because of AVF nonmaturation, the surgeon obtained a specimen of the AVF draining vein from the site of the new anastomosis, slightly proximal to the initial anastomotic site.

### Study Population

The University of Alabama at Birmingham (UAB) provides medical care for ~500 hemodialysis patients. Ten clinical nephrologists who are full-time members of the UAB Division of Nephrology provide medical care to these patients. Almost all patient hospitalizations, surgical procedures, and radiologic procedures occurred at UAB Hospital. Four transplant and vascular access surgeons performed the initial access surgery and subsequent surgical revisions. Members of the Department of Radiology performed radiologic diagnostic tests and interventions for dialysis access. All clinical information, including hospital discharge summaries, clinic notes, and surgical and radiologic reports, was available on an electronic medical record. Patients scheduled for a new AVF were invited to participate in this study. Approximately 90% of the patients approached agreed to enroll in the study.

### Preoperative Vascular Mapping

All patients underwent sonographic preoperative vascular mapping according to the standard UAB protocol.[2,8,17] Vascular measurements were performed with the patient in a seated position and the arm resting comfortably on an adjustable instrument stand. Arterial diameters were measured at the radial artery in the wrist and brachial artery in the antecubital fossa. A tourniquet was moved sequentially up the arm to measure venous diameters at several locations in the forearm and upper arm and evaluate for venous stenosis or thrombosis. Venography was performed in selected patients with clinical suspicion of central vein stenosis. All measurements were recorded on a worksheet, which was provided to the surgeon before the patient's preoperative visit. Creation of an AVF required a minimum arterial diameter of 2 mm and minimum venous diameter of 2.5 mm. If there were no suitable vessels for creation of a forearm AVF, the surgeon created an upper-arm AVF, if possible.

### Surgical Procedure

The transplant surgeons placed 3 types of upper-extremity AVFs, depending on the findings of the preoperative ultrasound: a radiocephalic (wrist) AVF, a brachiocephalic AVF, and a transposed brachiobasilic AVF. AVFs were created by performing direct anastomosis between the side of the artery and end of the vein. The surgeon obtained small specimens of the artery and vein used to create the AVF before performing the anastomosis. Specifically, these included a circumferential section of the vein and a partial (elliptical) section of the artery. Obtaining these samples was feasible in >90% of patients and did not result in postoperative complications. Rarely, the artery was too small for the surgeon to obtain a sample. Six patients with nonmaturing AVFs and a perianastomotic stenosis underwent subsequent surgical revision, at which time the surgeon obtained a specimen of the AVF draining vein at the site of the new anastomosis, which was slightly proximal to the prior anastomosis for pathologic examination.

### Pathologic Studies of Vascular Specimens

Cross-sections of arterial and venous samples were fixed in 10% neutral-buffered formalin and processed for light microscopy. A pathologist (S.L.) who was unaware of clinical information and AVF outcomes performed all histologic evaluations. All tissue samples were stained with hematoxylin and eosin and assessed for arterial medial fibrosis and arterial and venous intimal hyperplasia. Trichrome staining was performed to optimize visualization of medial fibrosis, with collagen staining blue and smooth muscle cells staining red. Medial fibrosis was quantified from the trichrome stain of the entire arterial specimen by using Bioquant Image Analysis (www.bioquant.com) to calculate the

**Table 1.** Clinical Features of the Study Population by Fistula Outcome

| | Nonmaturing AVFs | Mature AVFs | *P* |
|---|---|---|---|
| No. of patients | 19 | 31 | |
| Age (y) | 54 ± 16 | 55 ± 13 | 0.8 |
| Age ≥65 y | 5 (26) | 6 (19) | 0.6 |
| Women | 13 (68) | 12 (39) | 0.04 |
| Black | 12 (63) | 20 (64) | 0.9 |
| Diabetes | 10 (53) | 13 (42) | 0.5 |
| HTN | 18 (95) | 29 (94) | 0.9 |
| CAD | 2 (10) | 4 (13) | 0.8 |
| PVD | 1 (5) | 4 (13) | 0.8 |
| CVD | 2 (10) | 4 (13) | 0.8 |
| CHF | 5 (26) | 3 (10) | 0.1 |
| AVF located on forearm | 7 (37) | 9 (29) | 0.6 |
| AVF created after dialysis initiation | 10 (53) | 19 (61) | 0.7 |

*Note:* Age shown as mean ± standard deviation. Categorical variables shown as number (percentage).

Abbreviations: AVF, arteriovenous fistula; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; HTN, hypertension; PVD, peripheral vascular disease.

percentage of the vascular specimen staining blue. The internal elastic lamina demarcates the border between intima and media and usually is seen well on hematoxylin and eosin staining. In selected cases, elastic staining also was performed to better delineate the intima. The thickness of the vascular layer on the luminal side of the internal elastic lamina was used to assess intimal hyperplasia. Finally, von Kossa stain was used to detect medial microcalcification, which was graded by the pathologist on a semiquantitative scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The same pathologist also performed pathologic evaluation of specimens of the AVF draining vein from patients undergoing AVF surgical revision.

### Determination of AVF Suitability for Dialysis

AVF suitability for hemodialysis was defined as the ability to cannulate the AVF with 2 needles with dialysis blood flow ≥300 mL/min for at least 6 dialysis sessions in 1 month and within 6 months of AVF creation.[18] AVFs were deemed unsuitable for dialysis if they failed to achieve these criteria despite attempted salvage procedures to promote maturation. For patients who had not initiated dialysis therapy within 6 months of AVF creation, AVF suitability was determined in the first month after dialysis therapy was started. This definition has been validated repeatedly at UAB[2] and is similar to that used in a recent multicenter study.[6]

### Statistical Analysis

We assumed an AVF nonmaturation rate of 50% in patients with arterial medial fibrosis and 25% in those without arterial medial fibrosis. To provide statistical power of 80% to show a significant ($P < 0.05$) difference between the 2 groups, we needed to enroll 45 patients. Clinical, sonographic, and pathologic features were compared between patient subgroups using unpaired *t* tests for continuous variables and $\chi^2$ analysis for categorical variables. $P < 0.05$ was considered statistically significant.

## RESULTS

Our study consisted of 50 patients with CKD undergoing placement of a new AVF. Of these 50 study patients, 19 (38%) had AVF nonmaturation, whereas 31 (62%) had the AVF used successfully for dialysis at a median of 81 days after AVF creation. Those with nonmaturing AVFs were more likely to be women, but were similar in age, race, diabetes, hypertension, vascular disease, congestive heart failure, and AVF location to patients with an AVF that matured (Table 1). Almost 60% (29 of 50) of AVFs were placed after initiation of dialysis therapy, including 18 placed within the first year and 11 placed at later times. Preoperative arterial and venous diameters did not differ significantly between nonmaturing and mature AVFs in patients receiving a forearm AVF (Table 2). Preoperative arterial diameters were significantly smaller for upper-arm fistulas that failed to mature compared with those that matured (but still substantially greater than the minimal 2-mm diameter required by our protocol). However, venous diameters were similar in both groups of patients receiving an upper-arm fistula.

We did not observe intimal hyperplasia in any arterial specimen (Fig 1A and B). In contrast, medial fibrosis of varying degrees was observed in all arterial specimens obtained at the time of AVF creation. Medial fibrosis was quantified from trichrome stains of arteries (Fig 1C and D). Mean medial fibrosis for the study population was 64% ± 14% (range, 32%-90%) and did not differ significantly between nonmaturing and mature AVFs (Table 3). Arteries with ≥70% medial fibrosis were classified as having severe medial fibrosis. The proportion of patients with severe medial fibrosis did not differ between those with mature AVFs and

**Table 2.** Preoperative Sonographic Features of the Vasculature

| | Nonmaturing AVFs | Mature AVFs | *P* |
|---|---|---|---|
| No. of forearm fistulas | 7 | 9 | |
| Forearm arterial diameter (mm) | 3.0 ± 0.5 | 2.8 ± 0.3 | 0.4 |
| Forearm vein diameter (mm) | 2.9 ± 0.4 | 3.0 ± 0.4 | 0.9 |
| No. of upper-arm fistulas | 12 | 22 | |
| Upper-arm arterial diameter (mm) | 4.0 ± 0.8 | 5.2 ± 1.1 | 0.007 |
| Upper-arm vein diameter (mm) | 3.9 ± 1.3 | 4.6 ± 1.5 | 0.2 |

*Note:* Vascular diameters are measured at the level of AVF anastomosis.

Abbreviation: AVF, arteriovenous fistula.

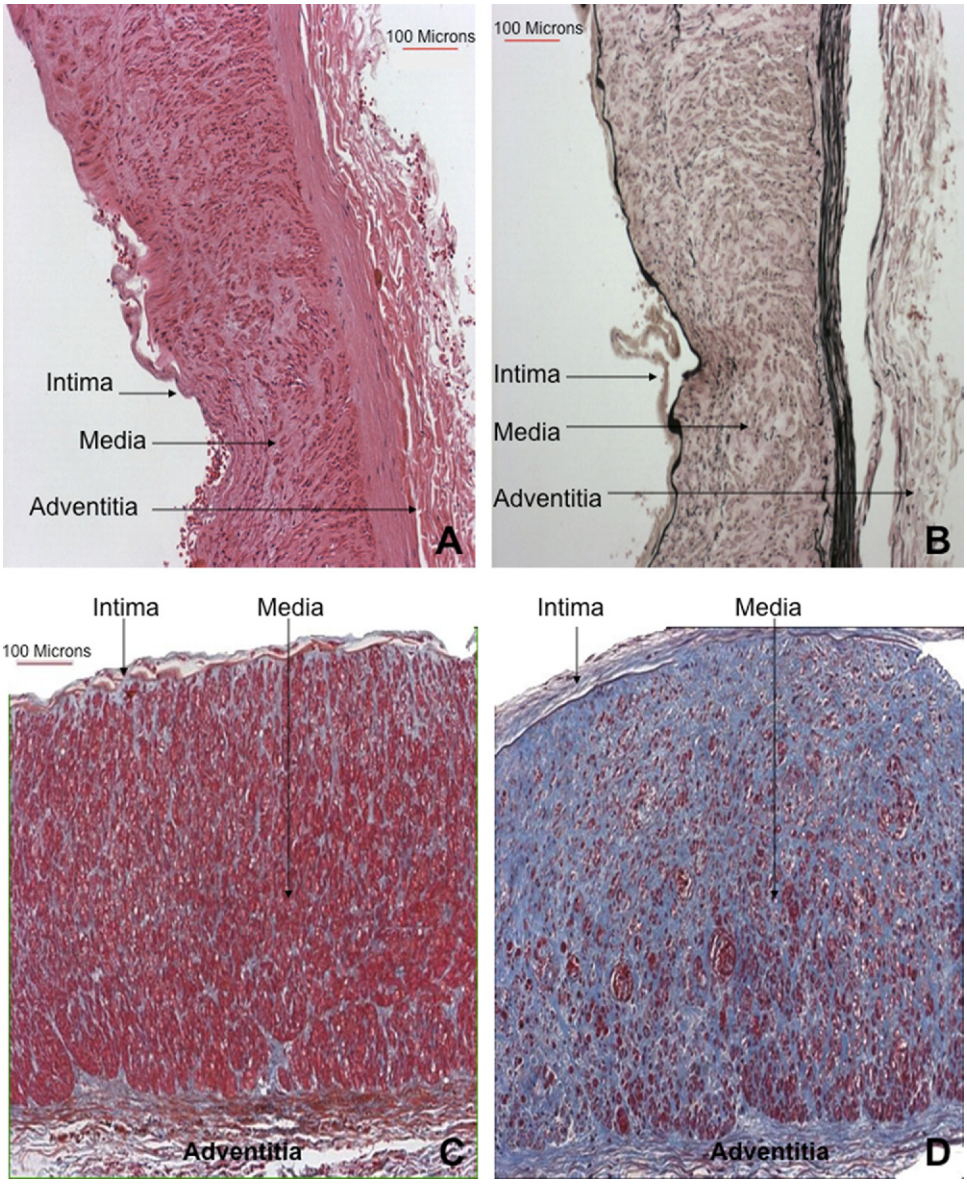


**Figure 1.** Histologic section of artery at time of fistula placement stained with (A) hematoxylin and eosin and (B) elastic van Gieson stain shows the 3 vascular layers. The internal elastic lamina separates the thin intima from the thick media. Trichrome stain shows an artery with (C) mild (32%) fibrosis (blue) and (D) significant (90%) fibrosis. The intimal layer is always thin.

those with nonmaturing AVFs. The frequency of severe medial fibrosis was greater in older patients and those with diabetes, but was not associated with sex, race, hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, or AVF location (Table 4).

Approximately two-thirds of the patients had arterial microcalcification, but the proportion did not differ significantly between those with mature and nonmaturing AVFs (Table 3). The magnitude of microcalcification was scored semiquantitatively on a scale of 0-3 (Fig 2A and B). Mean microcalcification scores were similar for arteries with severe medial fibrosis and those with milder medial fibrosis ($1.2 \pm 0.9$ vs $1.0 \pm 0.7$; $P = 0.6$). There was no significant difference in microcalcification scores in patients with mature and nonmaturing AVFs, although there was a trend ($P = 0.08$) for greater microcalcification in nonmaturing AVFs (Table 3).

None of the 50 venous samples obtained at AVF creation had evidence of significant intimal hyperplasia (Fig 2C). In 6 patients with nonmaturing AVFs, we obtained venous samples contiguous to the AVF anastomosis at both the time of AVF creation and 58-204 days later, when the AVF was surgically revised (without a prior angioplasty). These 6 patients had an anastomotic stenosis and had not undergone AVF angioplasty or cannulation before the surgical revision. All 6 patients were women, 3 had diabetes, age range was 33-76 years, 2 had ≥70% arterial medial fibrosis, and 2 had arterial microcalcification. Postoperative histologic examination of draining veins of nonmaturing AVFs showed severe neointimal hyperplasia in each case (Fig 2D) that had not

**Table 3.** Pathologic Features of Vascular Specimens

| | Nonmaturing AVFs | Mature AVFs | *P* |
|---|---|---|---|
| No. of patients | 19 | 31 | |
| Arterial medial fibrosis | 60 ± 14 | 66 ± 13 | 0.2 |
| Arterial medial fibrosis ≥70% | 5 (26) | 11 (35) | 0.5 |
| Arterial microcalcification present | 15 (79) | 19 (68)[a] | 0.6 |
| Arterial microcalcification score | 1.3 ± 0.8 | 0.9 ± 0.8 | 0.08 |
| Arterial intimal hyperplasia | 0 (0) | 0 (0) | 0.9 |
| Venous intimal hyperplasia | 0 (0) | 0 (0) | 0.9 |

*Note:* Continuous variables shown as mean ± standard deviation; categorical variables, as number (percentage).

Abbreviation: AVF, arteriovenous fistula.

[a]Tissue specimen inadequate in 3 patients with a mature AVF.

been present in the venous sample obtained at the time of AVF creation.

## DISCUSSION

Our study documented a high frequency of medial fibrosis in arteries used to create AVFs in patients with CKD. This observation is in keeping with a previous study documenting extensive medial fibrosis in patients with CKD, which is present in multiple vascular beds.[12] Successful AVF maturation requires arterial dilation.[7] Severe medial fibrosis may limit arterial dilation by increasing arterial stiffness because collagen is less distensible than smooth muscle.[19] On the basis of these observations, we had postulated that severe arterial medial fibrosis would be associated with AVF nonmaturation. Contrary to our hypothesis, severe medial fibrosis was not associated with AVF nonmaturation. There was a total disconnect between medial fibrosis and AVF outcomes. AVF nonmaturation was not associated with patient age or diabetes, although both variables were associated with severe medial fibrosis. Conversely, AVF nonmaturation was higher in women than men despite very similar degrees of severe medial fibrosis in both sexes. Although preoperative arterial diameters were larger in patients with a mature upper-arm AVF, this difference is unlikely to explain AVF maturation.[11]

Why might medial fibrosis not be associated with AVF nonmaturation? We propose 3 possible explanations. First, the vascular samples obtained might be too small to be representative of the entire artery used for AVF creation. Second, there could be alternative causes of increased arterial stiffness causing AVF nonmaturation in our study population. Thus, for example, differences in vascular reactivity, genetic polymorphisms, or medications also may affect AVF maturation, but were beyond the scope of the present study. Third, there may be poor correlation between arterial anatomy and function. Thus, a recent study applied a mathematical model to predict AVF blood flow and suggested that vascular dilatation may not be needed unless vascular diameters are small.[20]

Arterial calcification may decrease the distensibility of arteries, thereby adversely affecting AVF maturation. We observed microcalcification in a subset of arterial specimens, but the degree of microcalcification was not associated with medial fibrosis. There was a trend ($P = 0.08$) for higher microcalcification in nonmaturing fistulas, which might have been significant with a larger patient sample.

The pathologic abnormalities observed in the present study differ from those described by other investigators. In their series of 59 patients, Kim et al[14] described intimal hyperplasia in 76% of arteries used to create AVFs, and this pathologic abnormality was associated with shortened AVF survival. In contrast, we did not observe arterial intimal hyperplasia in our 50 patients. The difference in baseline arterial histologic characteristics between the 2 studies may be related to racial differences because the patients reported by Kim et al[14] were exclusively Asian, whereas ours were black or white. Two small studies described intimal hyperplasia in veins used to create AVFs, but neither reported the correlation between venous histologic characteristics and AVF outcomes.[15,16] In contrast, we did not observe intimal hyperplasia in any of the 50 veins used to create an AVF.

Whereas arteriovenous graft failure is clearly related to aggressive venous intimal hyperplasia at the vein-graft anastomosis,[21] the pathogenesis of AVF

**Table 4.** Clinical Features of Patients With and Without Severe Medial Fibrosis

| | Medial Fibrosis ≥70% | Medial Fibrosis <70% | *P* |
|---|---|---|---|
| No. of patients | 16 | 34 | |
| Age ≥65 y | 7 (44) | 4 (12) | 0.01 |
| Women | 7 (44) | 18 (53) | 0.5 |
| Black | 8 (50) | 24 (70) | 0.2 |
| Diabetes | 10 (62) | 13 (38) | 0.01 |
| HTN | 16 (100) | 31 (91) | 0.2 |
| CAD | 2 (12) | 4 (12) | 0.9 |
| PVD | 2 (12) | 3 (9) | 0.7 |
| CVD | 3 (19) | 3 (9) | 0.3 |
| CHF | 1 (6) | 7 (20) | 0.2 |
| AVF located on forearm | 5 (31) | 11 (32) | 0.9 |

*Note:* Categorical variables as number (percentage).

Abbreviations: AVF, arteriovenous fistula; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; HTN, hypertension; PVD, peripheral vascular disease.

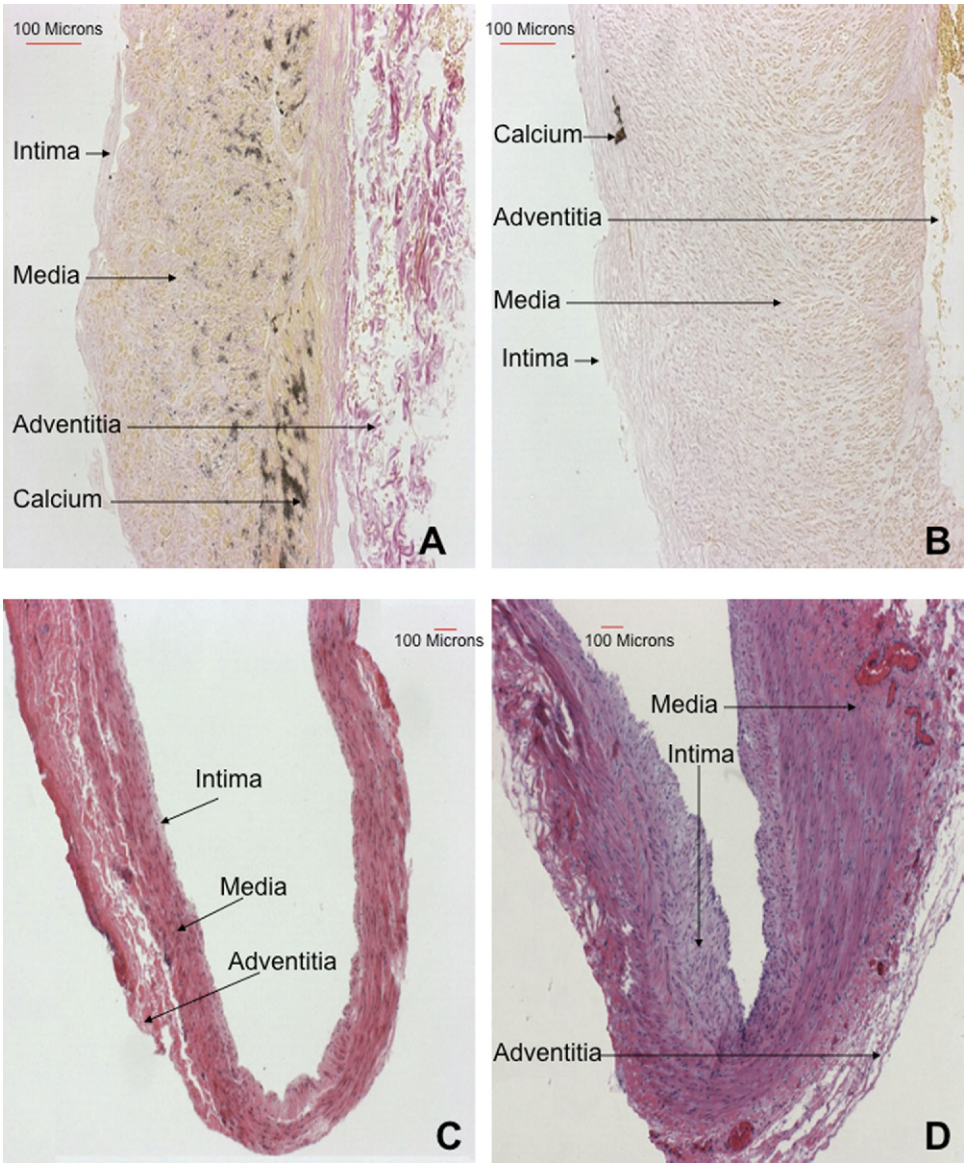


**Figure 2.** von Kossa stain (calcium salt stains black) of artery with (A) heavy and (B) minimal calcification. It is common for minimal calcification to be deposited predominantly in the internal elastic lamina. (C) Vein stained with hematoxylin and eosin at original fistula placement shows thin intimal layer; (D) at reoperation 115 days after fistula creation, severe neointimal hyperplasia has developed.

nonmaturation is poorly understood.[22] Roy-Chaudhury et al[13] recently reported the presence of severe intimal hyperplasia in 4 patients with nonmaturing AVFs, but could not verify whether venous lesions were pre-existing or developed after AVF creation. A preliminary report from the same group reported pre-existing intimal hyperplasia in 10 of 12 veins used for AVF creation,[16] but did not report whether this abnormality predicted AVF nonmaturation. In the present study, we showed the presence of severe venous neointimal hyperplasia in 6 patients with nonmaturing AVFs that clearly was not present in venous samples obtained at the time of AVF creation. These paired observations strongly suggest that venous intimal hyperplasia develops de novo after AVF creation, although the cellular mechanism leading to it remains to be elucidated.

In summary, we have observed frequent arterial medial fibrosis in upper-extremity arteries used to create AVFs in patients with CKD. However, this vascular abnormality does not appear to be responsible for the pathogenesis of AVF nonmaturation. Arterial microcalcification may be predictive of AVF nonmaturation, although a larger sample would be required to confirm this hypothesis. Contrary to prior reports, venous intimal hyperplasia was not found in our patients at the time of AVF creation. Severe intimal hyperplasia was observed at subsequent AVF revision for anastomotic stenosis, suggesting de novo neointimal hyperplasia development in these immature AVFs.

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