Preoperative Venous Intimal Hyperplasia, Postoperative Arteriovenous Fistula Stenosis, and Clinical Fistula Outcomes

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Summary

Background and objectives Arteriovenous fistulas often fail to mature, and nonmaturation has been attributed to postoperative stenosis caused by aggressive neointimal hyperplasia. Preexisting intimal hyperplasia in the native veins of uremic patients may predispose to postoperative arteriovenous fistula stenosis and arteriovenous fistula nonmaturation.

Design, setting, participants, & measurements This work explored the relationship between preexisting venous intimal hyperplasia, postoperative arteriovenous fistula stenosis, and clinical arteriovenous fistula outcomes in 145 patients. Venous specimens obtained during arteriovenous fistula creation were quantified for maximal intimal thickness (median thickness=22.3 μm). Postoperative ultrasounds at 4–6 weeks were evaluated for arteriovenous fistula stenosis. Arteriovenous fistula maturation within 6 months of creation was determined clinically.

Results Postoperative arteriovenous fistula stenosis was equally frequent in patients with preexisting venous intimal hyperplasia (thickness>22.3 μm) and patients without hyperplasia (46% versus 53%; P=0.49). Arteriovenous fistula nonmaturation occurred in 30% of patients with postoperative stenosis versus 7% of those patients without stenosis (hazard ratio, 4.33; 95% confidence interval, 1.55 to 12.06; P=0.001). The annual frequency of interventions to maintain arteriovenous fistula patency for dialysis after maturation was higher in patients with postoperative stenosis than patients without stenosis (0.83 [95% confidence interval, 0.58 to 1.14] versus 0.42 [95% confidence interval, 0.28 to 0.62]; P=0.008).

Conclusions Preexisting venous intimal hyperplasia does not predispose to postoperative arteriovenous fistula stenosis. Postoperative arteriovenous fistula stenosis is associated with a higher arteriovenous fistula nonmaturation rate. Arteriovenous fistulas with hemodynamically significant stenosis frequently mature without an intervention. Postoperative arteriovenous fistula stenosis is associated with an increased frequency of interventions to maintain long-term arteriovenous fistula patency after maturation.


Introduction

Although arteriovenous fistulas (AVFs) are considered to be the preferred form of vascular access for hemodialysis, their successful use is limited by the high rate (up to 60%) of AVF nonmaturation (1,2). Unfortunately, there is limited understanding of the pathogenesis of AVF nonmaturation. Observations from animal models of AVF have documented rapid onset of venous intimal hyperplasia near the anastomosis, and this lesion has been postulated to contribute to AVF nonmaturation (3–6). Limited human data have reported severe venous intimal hyperplasia in the juxta-anastomotic region of nonmaturing AVF undergoing surgical salvage procedures (7,8). Finally, venous intimal hyperplasia has been described in mature AVFs that develop stenosis of the draining vein (9).

More recently, preexisting intimal hyperplasia has been observed in the native veins used to create an AVF in CKD patients (10,11). It is possible that preexisting venous intimal hyperplasia predisposes those patients to more aggressive venous neointimal hyperplasia after AVF creation, thereby contributing to AVF stenosis and presumably, AVF nonmaturation and inferior long-term AVF outcomes. To test this hypothesis, we performed a prospective observational study to evaluate the association between preexisting venous intimal hyperplasia, postoperative AVF stenosis, and clinical AVF outcomes in a cohort of CKD patients.

Materials and Methods

Summary of Procedures

We enrolled 145 patients with CKD scheduled for AVF surgery between October 1, 2008 and April 30, 2012. This group included 50 patients previously reported in another publication (8). The patients underwent preoperative sonographic vascular mapping,
and the surgeons used these results to plan the vascular access procedure. Patients were invited to participate in this research project at the time of their preoperative visit, and they provided informed consent for the protocol approved by our local Institutional Review Board. Before creating the arteriovenous anastomosis, the surgeon obtained a small specimen of the vein for pathologic studies. A pathologist quantified the maximal intimal thickness for each venous sample. The patients underwent routine ultrasounds 4–6 weeks after surgery to assess AVF maturation and presence of stenosis. Subsequently, we determined for each patient whether the AVF matured successfully to be used for dialysis, the duration of unassisted primary AVF patency after maturation, and the frequency of interventions to maintain long-term patency for dialysis after AVF maturation. Finally, we evaluated the association between preexisting venous intimal hyperplasia, postoperative AVF stenosis, and clinical AVF outcomes.

Preoperative Vascular Mapping
Each patient underwent standardized preoperative sonographic vascular mapping before seeing the surgeon (12,13). This evaluation determined the size of the vessels and assessed for the presence of stenosis or thrombosis in the veins. The minimal criteria for creation of an AVF included an arterial diameter ≥2 mm, venous diameter ≥2.5 mm, and absence of stenosis or thrombosis in the draining vein. The AVF was created preferentially in the forearm. However, if the forearm vessels were unsuitable, the surgeon created an upper arm AVF.

Surgery
The surgeon reviewed the preoperative vascular mapping to determine the optimal vascular access for each patient. Patients received one of three types of vascular access: a radiocephalic AVF, a brachiocephalic AVF, or a transposed brachiobasilic AVF. At the time of surgery, a small specimen of the vein used for AVF creation was obtained for subsequent pathologic evaluation. The surgeons routinely saw the patients for postoperative visits 1–2 weeks after AVF creation.

Postoperative AVF Management
AVFs that thrombosed within the first month were deemed unsalvageable, and those patients were considered for placement of a new vascular access. A postoperative ultrasound of the AVF was obtained 4–6 weeks after surgery if the AVF had not thrombosed earlier (14,15). The ultrasound evaluated the diameter of the AVF, blood flow rate, depth of the AVF from the skin, and presence of stenosis. An AVF was considered to have hemodynamically significant juxta-anastomotic stenosis if there was visually evident focal stenosis within 2 cm of the anastomosis and the ratio of peak systolic velocity pre- and poststenosis was ≥3:1 (14). The AVF was considered to have a hemodynamically significant draining vein stenosis if there was a visually evident focal stenosis ≥2 cm cephalad to the anastomosis and the ratio of peak systolic velocity pre- and poststenosis was ≥2:1. AVF were considered sonographically immature if the diameter was <4 mm or the access blood flow was <500 ml/min. Immature AVF with discrete anatomic lesions (juxta-anastomotic or draining vein stenosis or accessory veins) was referred for percutaneous or surgical access procedures to promote AVF maturity (15).

No interventions were performed in AVFs that were sonographically mature, even if the ultrasound revealed stenosis or accessory veins. If an AVF was excessively deep, the surgeon performed a superficialization procedure. Clinically mature AVFs were cannulated at 8 weeks postoperatively. After they were being successfully cannulated for dialysis, AVFs were monitored clinically for evidence of stenosis (16). If stenosis was suspected, the patient was referred for a diagnostic fistulogram. If imaging confirmed a >50% stenosis, the AVF underwent angioplasty. Thrombosed fistulas underwent percutaneous or surgical thrombectomy. If it was unsuccessful, the AVF was considered to have failed permanently.

Pathologic Studies
The vein samples collected at the time of AVF surgery were placed in formalin. Thin sections were stained with hematoxylin and eosin. A pathologist (S.L.) who was unaware of the clinical information or AVF outcomes examined the specimens. He quantified the maximal venous intimal thickness, which was measured between the vascular endothelium and the internal elastic lamina (Figure 1). The venous specimens were adequate to measure intimal thickness in 129 patients.

AVF Outcomes
An AVF was considered to be clinically mature if it could be successfully cannulated with two needles to provide a dialysis blood flow ≥300 ml/min for 1 month within 6 months after its creation (8). If the patient had not yet started dialysis, AVF maturation was determined in the first 2 months after initiation of dialysis. An AVF was considered to be nonmaturing if it was not suitable for dialysis use within 6 months of its creation, despite attempted salvage procedures. Unassisted primary AVF survival was calculated as the time until the first AVF intervention (angioplasty, thrombectomy, or surgical revision) after its successful cannulation for dialysis. Effective secondary AVF survival was calculated from the time of successful cannulation until permanent loss of patency, despite salvage procedures. Finally, we calculated the frequency of interventions after AVF maturation to maintain long-term patency for dialysis.

Statistical Analyses
Continuous variables were compared using t tests, and categorical values were compared by chi-squared tests. Standard survival techniques were used to calculate AVF survival, and differences between survival curves were assessed by the log-rank test. The frequency of AVF interventions was evaluated by Poisson tests. A P value <0.05 was considered statistically significant.

Results
Of 145 patients enrolled in the study, we were able to obtain suitable venous samples at the time of AVF creation in 129 patients. Early thrombosis (before the
postoperative AVF ultrasound) occurred in 16 patients, leaving 113 patients for subsequent analysis. We quantified the maximal intimal thickness of native vein specimens obtained by the surgeon at the time of AVF creation. The median intimal thickness was 22.3 μm (total range=1–279 μm; interquartile range [IQR]=13.2–45.4 μm), and for the purpose of statistical analysis, patients were divided into patients with intimal thickness above and below the median. These two patient groups were similar in age, sex, race, diabetes, hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and congestive heart failure (Table 1). Compared with those patients with forearm AVFs, patients with upper arm AVFs were more likely to have venous intimal hyperplasia (intimal thickness >22.3 μm). The median venous intimal thickness was higher for upper arm veins compared with forearm veins (23.5 μm [IQR=15.5–49.2 μm] versus 16.4 μm [IQR=7.8–25.4 μm]; P=0.003). The preoperative arterial and venous diameters did not differ between patients with and without venous intimal hyperplasia (Table 2). Moreover, there was no significant correlation between the preoperative vein intimal thickness and the preoperative vein diameter (Spearman R=0.13; P=0.14).

A postoperative ultrasound was performed 4–6 weeks after AVF creation in 113 patients. It revealed a hemodynamically significant stenosis in 56 patients or 50% of the total. There were 43 patients with a juxta-anastomotic stenosis, 15 patients with a draining vein stenosis, and 2 patients with stenoses at both locations. No feeding artery stenoses were seen on ultrasound. The frequency of postoperative stenosis was similar in those patients with and without preexisting venous intimal hyperplasia (46% versus 53%; P=0.49) (Table 3). The lack of association between preexisting venous intimal hyperplasia and postoperative stenosis remained true when forearm and upper arm fistulas were analyzed separately. In addition, there was no significant association between preoperative intimal hyperplasia and postoperative stenosis, even when the location of the stenosis was considered. Thus, a postoperative juxta-anastomotic stenosis was present in 29% of patients with preexisting venous intimal hyperplasia versus 42% of those patients without this lesion (P=0.18). Likewise, a

Table 1. Clinical features of patients with and without preexisting venous intimal hyperplasia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vein Intima &gt;22.3 μm</th>
<th>Vein Intima ≤22.3 μm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N points</td>
<td>64</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Age ≥65 yr</td>
<td>14 (22%)</td>
<td>15 (23%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Men n</td>
<td>36 (56%)</td>
<td>32 (49%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Black race</td>
<td>47 (73%)</td>
<td>39 (60%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30 (47%)</td>
<td>29 (45%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (92%)</td>
<td>59 (91%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9 (14%)</td>
<td>5 (8%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>7 (11%)</td>
<td>4 (6%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5 (8%)</td>
<td>7 (11%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>13 (20%)</td>
<td>10 (15%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Forearm fistula</td>
<td>15 (23%)</td>
<td>29 (45%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Upper arm fistula</td>
<td>49 (77%)</td>
<td>36 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. | Hematoxylin and eosin stains illustrating venous intimal hyperplasia. The maximal intimal thickness was measured between the internal elastic lamina and the vascular lumen. A illustrates a vein without intimal hyperplasia (thickness=7.8 μm), and B illustrates a vein with severe intimal hyperplasia (thickness=86.4 μm).
postoperative draining vein stenosis was present in a similar proportion of patients with and without preexisting venous intimal hyperplasia (12% versus 9%; P = 0.57).

We subsequently evaluated the association between postoperative AVF stenosis and clinical AVF maturation. AVF nonmaturation was observed in 30% of patients with a juxta-anastomotic stenosis but only 7% of patients without any AVF stenosis (hazard ratio, 4.33; 95% confidence interval [95% CI], 1.55 to 12.06; P = 0.001) (Table 4). The predictive value of postoperative AVF stenosis for AVF nonmaturation differed by AVF location, being 50% for forearm fistulas but only 18% for upper arm AVFs (P = 0.01). When the analysis was restricted to juxta-anastomotic stenosis, AVF nonmaturation was observed in 32% of all patients with postoperative stenosis versus 10% of patients without stenosis (P = 0.003). When the analysis was restricted to draining vein stenosis, the rate of AVF nonmaturation was similar in patients with and without postoperative stenosis (27% versus 17%; P = 0.39).

Unassisted primary AVF survival (time to first salvage procedure after maturation) was similar in patients with and without AVF stenosis shown in the postoperative ultrasound (hazard ratio, 1.38; 95% CI, 0.70 to 2.88; P = 0.33) (Figure 2). The median AVF survival in the two groups was 354 and 562 days, respectively.

There were 63 interventions (angioplasty, thrombectomy, or surgical revision) performed to maintain AVF patency after maturation during 106.1 patient-years of follow-up for a frequency of 0.59 (95% CI, 0.46 to 0.78) procedures per year. The frequency of interventions was twofold higher in patients whose 4- to 6-week postoperative AVF ultrasound revealed a stenosis (0.83; 95% CI, 0.58 to 1.14 per year) compared with patients without postoperative AVF stenosis (0.42; 95% CI, 0.28 to 0.62; P = 0.008).

**Discussion**

Our current understanding of the pathogenesis of AVF nonmaturation is that it is most commonly caused by postoperative AVF stenosis, which in turn, is caused by aggressive neointimal hyperplasia after AVF creation. Moreover, it has been postulated that preexisting intimal hyperplasia in the veins used to create an AVF may predispose to accelerated postoperative neointimal hyperplasia, leading to more frequent stenosis and AVF nonmaturation (11). The present study permitted us to test these hypotheses by exploring the relationship between preexisting venous intimal hyperplasia and postoperative AVF stenosis. We expected to find a higher frequency of postoperative AVF stenosis in those patients with preexisting venous intimal hyperplasia. Our observations did not support this hypothesis. If anything, the frequency of postoperative stenosis tended to be lower in patients with preexisting venous intimal hyperplasia than in patients without hyperplasia.

We confirmed a significant association between postoperative AVF stenosis and AVF nonmaturation, suggesting a causal relationship. The negative predictive value of...
postoperative stenosis was excellent. The AVF matured in 93% of patients without postoperative AVF stenosis. In contrast, the positive predictive value of postoperative AVF stenosis was fairly modest: only 30% of patients with postoperative stenosis had nonmaturing AVF. Moreover, the predictive value of postoperative stenosis for AVF nonmaturation was substantially lower in upper arm AVF compared with forearm AVF (18% versus 50%), perhaps reflecting the higher flow rate in more proximal AVFs. In other words, the majority (over two thirds) of new AVFs matured, despite sonographic evidence for postoperative stenosis and no prophylactic intervention to repair the stenosis. Previous reports have observed a high frequency of juxta-anastomotic or draining vein stenosis in immature AVFs, with angioplasty converting many of them to mature AVFs (17,18). Taken together, these findings suggest that stenosis is necessary but not sufficient for the pathogenesis of AVF nonmaturation. Clearly, there are other biologic or hemodynamic features that allow an AVF to mature, even when stenosis is present.

The location of AVF stenosis varies according to the AVF age. The stenosis is typically in the juxta-anastomotic region in nonmaturing AVFs, with fewer stenoses observed in the draining vein. In the current study, 74% of the stenoses detected by the postoperative ultrasound were in the juxta-anastomotic region. Conversely, draining vein stenosis is more frequent when AVF dysfunction develops at later time periods (after successful cannulation). However, stenosis at both locations seems to be mediated by neointimal hyperplasia (7–9). Given the common biologic pathway, it is not surprising that we observed a higher frequency of interventions to maintain long-term AVF patency in patients whose AVF initially matured but subsequently required treatment of a postoperative AVF stenosis that developed or worsened after maturation. Although unassisted primary AVF patency tended to be shorter in patients with postoperative AVF stenosis, this difference did not achieve statistical significance, likely because of the relatively low event rate of AVF dysfunction after clinical maturation.

The strengths of the present study include prospective data collection, documentation of the pathology of the vein used to create an AVF by a pathologist who was unaware of the clinical AVF outcomes, routine postoperative ultrasounds obtained before attempted AVF cannulation, and use of standard definitions of AVF nonmaturation. Our study also has some limitations. First, it was a single-center study, and the results may not generalize to all dialysis centers. For example, the rate of vascular disease in our study population was lower than the rate present in the national dialysis population, and this difference may affect the results. Second, we did not obtain routine angiography to confirm the juxta-anastomotic or draining vein stenosis suggested by the postoperative ultrasound. However, we have previously reported the accuracy of ultrasound for noninvasive surveillance of access stenosis (14). Third, we did not obtain subsequent vascular specimens to show the presence of neointimal hyperplasia in patients with sonographically shown juxta-anastomotic AVF stenosis. However, limited human data have shown aggressive intimal hyperplasia in immature AVF undergoing surgical revision (7,8). Fourth, we did not obtain immunohistochemical staining of the vein samples to show the presence of myofibroblasts and smooth muscle cells, which would further corroborate the presence of venous intimal hyperplasia.

In summary, we did not find an association between preexisting venous intimal hyperplasia and postoperative AVF stenosis. This negative finding suggests a different biologic pathway for preexisting intimal hyperplasia in the native veins of uremic patients compared with neointimal hyperplasia in the juxta-anastomotic region.
hyperplasia that develops after AVF creation. Thus, one should exercise caution in extrapolating the potential importance of preexisting vascular pathology in the pathogenesis of AVF nonmaturation. Also, we have shown that, although stenosis is an important factor in the pathogenesis of AVF nonmaturation, there are clearly additional factors contributing to AVF nonmaturation, which have yet to be defined.

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Disclosures

None.

References


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