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Vascular 2010 18: 316
DOI: 10.2310/6670.2010.00054

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What is This?
Management of the Immature Autogenous Arteriovenous Fistula

Theodore F. Saad, MD*

A high-quality autogenous arteriovenous fistula provides the optimal access for hemodialysis. Following initial surgical construction of a fistula, the maturation process is driven by hemodynamic, cellular, and humoral factors that must result in increased blood flow, vessel dilation, and thickening of the vessel wall before the fistula can be successfully used for dialysis needle access. Different demands are placed on each fistula depending on the individual patient’s hemodialysis requirements, which must be clearly understood to properly assess and treat the immature fistula. When spontaneous maturation fails to achieve a functional fistula, additional surgical or minimally invasive interventional procedures may be necessary to enhance the maturation process. Various techniques have been reported to achieve successful fistula maturation. The purpose of this article is to review the concepts of fistula maturation and the interventions that may be performed in cases where there is failure to mature spontaneously.

Key words: arteriovenous fistula, hemodialysis, maturation

Fistula maturation is a general term used to refer to multiple processes that occur from the time of surgical fistula construction until the time the arteriovenous fistula (AVF) becomes suitable for reliable hemodialysis needle access. The desired end result of the maturation process is a high-flow, large-caliber, superficial vessel with robust wall structure suitable for reliable, repeated large-bore dialysis needle access. Criteria for assessment of maturation have been proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) as the “rule of sixes.” This stipulates that by 6 weeks after surgical creation, the fistula should measure 6 mm diameter or greater, 6 mm or less deep from the skin surface, and 600 mL/min or greater blood flow. This author would also include a criterion for greater than 6 cm usable length. These parameters are relatively easy to quantify and provide a practical starting point for assessment of fistula maturity. However, several less easily quantified factors may be important in achieving a mature fistula. These include patient needle tolerance, staff technical skill, availability of buttonhole needle access, quality and integrity of the skin and soft tissues, body habitus, and location of the fistula.

Fistula maturation must be assessed in the context of what constitutes adequate or optimal hemodialysis. The urea kinetic model is widely used to measure the “dose” of hemodialysis based upon blood urea nitrogen (BUN) as a “surrogate” for low-molecular-weight uremic toxins. Urea removal is typically estimated by the urea reduction ratio based upon BUN concentration immediately prior to (BUNpre) and following (BUNpost) a dialysis session, defined as:

\[
URR = \left[1 - \frac{\text{BUN}_{\text{pre}} - \text{BUN}_{\text{post}}}{\text{BUN}_{\text{pre}}}\right] \times 100
\]

Alternatively, this can be expressed as \( K_{\text{urea}} \times t_d / V_{\text{urea}} \) (Kt/V), the fraction of total body urea space fully cleared of urea during a dialysis session, where \( K_{\text{urea}} \) is the effective dialyzer urea clearance (mL/min), \( t_d \) is dialysis treatment time (min), and \( V_{\text{urea}} \) is the urea volume of distribution (mL), which approximates total body water. Urea clearance necessary to provide adequate dialysis is generally defined as the URR equal to 65% or Kt/V equal to 1.2, although higher targets of 70% and 1.4, respectively, are recommended by the KDOQI to achieve optimal dialysis outcomes. It is also important to note that for any given dialyzer, the maximum theoretical value of \( K_{\text{urea}} \) is equal to the blood pump speed,
assuming that 100% of the delivered urea is removed through the dialyzer. In practice, $K_{\text{urea}}$ is always lower than the blood pump speed, and this fraction is further decreased at higher blood pump speeds. To achieve maximal clearance parameters, the fistula must be able to deliver sufficient blood to fill the blood pump and avoid recirculation; generally, this requires a fistula blood flow rate 50% greater than the dialysis blood pump rate.

In practical terms, this means that the volume cleared ($K_{\text{urea}} \beta_d$) during a dialysis session must equal 1.4 times the patient’s total body water volume. Thus, for a patient who weighs 50 kg, $V_{\text{urea}}$ equals approximately 30,000 mL and $K_{\text{urea}} \beta_d$ must equal 42,000 mL. With a 240-minute dialysis session, this requires that $K_{\text{urea}}$ equal 175 mL/min, which can be readily achieved using small needles (eg, 17 gauge) and a blood pump speed of 200 mL/min blood flow. Even a low-flow fistula running at 300 mL/min would be sufficient to provide adequate hemodialysis access for this patient. Alternatively, a 100 kg patient who requires twice the clearance during the same 240-minute treatment requires that $K_{\text{urea}}$ equal 350 mL/min. Owing to diminished dialyzer and blood pump efficiency at higher flow rates, this demands a pump speed of 400 to 450 mL/min, which, in turn, demands larger dialysis needles (eg, 15 gauge) and higher fistula flow rates (greater than 600 mL/min). Any further increase in body size or decrease in dialysis efficiency will put proportionately greater flow and needle size demands on the fistula. Of course, lengthening the dialysis treatment time is always an effective means of increasing urea clearance. This option must be considered when necessary and arguably is the most effective and appropriate means of enhancing dialysis clearance. For better or for worse, in the United States, our patients and our system are accustomed to 4-hour treatments; longer treatment times often create hardships for patients and dialysis centers. Persuading a patient that he or she needs to stay on dialysis for 5 hours may be challenging when other patients are receiving 4-hour treatments. For eligible patients, nocturnal, home, or daily hemodialysis modalities allow for increased urea clearance without requiring exceptionally high fistula flow rates or dialyzer clearances. Thus, it is clear that the concept of fistula “maturity” must be viewed in the context of the individual patient’s dialysis requirement and prescription. A fistula that is mature and functional for one patient may be marginal or wholly inadequate for another. Inserting two needles and running the pump for 4 hours does not prove that the fistula is capable of providing optimal vascular access even if it is deemed to be “mature.”

The first step in the process of creating a high-quality functional AVF is a well-performed surgical construction using the optimal artery-vein pair based on appropriate clinical and/or ultrasound preoperative vascular assessment. Konner and colleagues described in detail the technical factors that contribute to high fistula success rates in their program. Recent clinical practice guidelines from the Society for Vascular Surgery detail the important considerations in surgical placement of arteriovenous hemodialysis access. Following surgical fistula construction, there are hemodynamic, cellular, and humoral processes that lead to vascular remodeling and adaptation over time. These changes are induced in part by shear stress on endothelial cells, resulting in nitric oxide and prostacyclin–mediated vasodilation. In addition, numerous endothelial cell transcription factors are activated. Typically, this will result in spontaneous fistula dilation and hypertrophy of the vessel wall such that the patient will achieve a functional fistula without requirement for any external assistance (Figure 1). Unfortunately, a substantial fraction of fistulae fail to mature despite efforts to select suitable patients, use preoperative mapping to identify the best quality available vessels, and execute a technically successful operation.

Numerous reports demonstrate poor patency rates of native AVF. Rooijens and colleagues reported the results from multiple pooled studies of radiocephalic AVF and found a primary failure rate of 15.3%, primary patency of 62.5%, and secondary patency of 66.0%. A recent article by Biuckians and colleagues described 1-year primary and secondary patency rates of 36% and 55%, respectively. Dember and colleagues performed a randomized prospective trial of clopidogrel versus placebo for prevention of early fistula failure in 877 patients at nine centers undergoing new fistula construction. Although early
thrombosis rates were reduced in the clopidogrel group (12.2% vs 19.5% in controls), there was no difference in fistula maturation, as defined by “suitability for dialysis,” with failure rates of 61.8% and 59.5% in the two groups, respectively. This very high failure rate occurred despite application of surgical or percutaneous interventions to enhance fistula maturation.

Timing is a critical factor in the development of a mature and functional fistula. The increase in blood flow and process of adaptive remodeling occur very early after surgical fistula construction. Therefore, signs of successful maturation should be evident within 4 weeks of surgery, and it is important that every fistula be carefully assessed at this point. Assessment begins with a thorough physical examination looking for evidence of high flow (ie, strong palpable thrill), vein dilation, signs of stenosis, and the presence of competing accessory veins. Duplex ultrasonography may be used to clarify and enhance physical examination findings. Ultimately, for most AVF that do not demonstrate signs of optimal early maturation, radiographic imaging is warranted to fully define all the relevant anatomy from the artery through the central veins, with the potential for percutaneous intervention.

Some practitioners tend to wait for inordinate periods of time in the hope that early fistula nonmaturation will improve over months or even years and ultimately result in a functional, mature fistula. There is no evidence to support such a protracted maturation phase. Furthermore, for patients who are receiving hemodialysis treatment via venous catheter access, excessively long waiting times for fistula maturation expose them to high risks of catheter-related infection and central vein stenosis or thrombosis. Spontaneous fistula maturation should be clearly evident by 4 weeks postoperatively. If there is evidence for delayed maturation, it is essential to obtain appropriate fistula imaging and proceed with interventions as required to expediously advance fistula maturation.

The matter of physical training to enhance fistula maturation deserves special mention. NKF-KDOQI guidelines recommend in favor of hand exercises, repeatedly squeezing a rubber ball to increase arterial blood flow and vessel size in maturing fistulae. This recommendation is based on two small studies involving 23 and 14 patients, respectively, who demonstrated enlargement of radial artery and maximal vein diameters after a variable period of programmed hand exercises. This has never been validated by a clinical trial demonstrating improvement in fistula outcomes. There has long been a mythical role of the “red rubber ball” in fistula maturation. Many of us were trained as fellows decades ago when this was about all

we had to offer for fistula maturation. One could argue that this practice is at least inexpensive and harmless and so might as well be adopted. There are the potential benefits that this activity may call patients’ attention to their fistula, encourage them to self-assess for signs of fistula maturation, and take an early, active role in the assessment and care of their “lifeline.” A contrary view, however, holds that the red rubber ball is a distraction from what is really important. If the fistula is destined to mature based on favorable anatomic and physiologic parameters, then it will mature with or without adjunctive exercise. Conversely, if a fistula is destined to maturation failure owing to unfavorable anatomic parameters, then hand exercise is unlikely to help; that is, juxta-anastomotic stenosis will not respond to exercise. Finally, there may be a tendency for some providers to blame the patient for fistula failure based on that patient’s presumably inadequate ball-squeezing regimen. This should be avoided when, in fact, successful maturation is primarily dependent on anatomic, surgical, or interventional deficiencies.

When faced with a nonmaturing fistula, one must determine which, if any, interventions are warranted to enhance fistula maturation. Possible interventions include balloon angioplasty of discrete stenotic lesions involving inflow (eg, juxta-anastomotic segment) or outflow (eg, transposed vein swing point or cephalic arch); balloon dilation of inadequately developed vein, including the intended puncture segment (balloon maturation); obliteration of competing accessory veins using surgical ligation or percutaneous coil embolization techniques; or surgical revision such as reconstruction of the arteriovenous anastomosis. This list would also technically include surgical vein transposition, but this component of access construction is an essential aspect of either initial or staged fistula creation; as such, it is more appropriately considered part of the surgical technique rather than a maturation issue. It is important to recognize that not every immature fistula can be salvaged and, in some cases, it may be preferable to abandon a fistula with little hope of successful maturation. This decision must be weighed against alternative arteriovenous access options for each patient; if there is little prospect of creating a better quality fistula, more aggressive maturation measures may be warranted. If, however, the patient with a very poor quality fistula has arterial and venous anatomy well suited to construction of a new high-quality fistula elsewhere (Figure 2), the interventional physician and vascular surgeon should consider this before embarking on a series of interventions likely destined to fail or at best create a marginal, high-maintenance, low-performing fistula. This is especially true for a patient likely
to require very high dialysis blood flows to achieve adequate clearance. Certain clinical and anatomic parameters have been found to correlate with fistula maturation; however, there are few data to help identify which established immature fistulae will respond favorably to maturation assistance maneuvers.

Recently, Voormolen and colleagues reported meta-analysis on multiple studies of fistula nonmaturation. The results pooled from 12 reports comprising 745 patients treated for fistula nonmaturation using a variety of percutaneous and surgical methods demonstrated an 86% success rate in achieving a functional fistula. Primary and secondary patency rates from a subset of these articles were 51% and 76%, respectively. Several of the individual studies reviewed in this meta-analysis warrant particular attention. Beathard and colleagues reported the results of treatment of 100 AVF with failure of spontaneous maturation. All 100 cases demonstrated abnormalities that were determined to be clinically significant and warranting treatment. A variety of percutaneous interventions were performed, including combinations of venous angioplasty, arterial angioplasty, and accessory vein obliteration. Successful fistula function was achieved in 92% of patients, with 68% remaining functional at 12 months. In 12 cases, the only lesion identified was an accessory vein; the results of treatment and long-term function in this subgroup were not reported separately. Falk reported the results of treatment in 65 nonmaturing fistulae; 113 procedures were performed (1.7 per fistula), resulting in 74% functional fistulae. A high rate of interventions was also reported for 63 mature functional fistulae, requiring 1.75 procedures per access-year to maintain fistula function. Nassar and colleagues reported a series of 119 patients with failure to mature AVF. These patients were treated with angioplasty of the artery in 6 cases (5.1%), arterial anastomosis in 56 cases (47.1%), juxta-anastomotic segment in 35 cases (29.4%), peripheral vein in 70 cases (58.8%), and central vein in 10 cases (8.4%). Accessory veins were treated in 35 cases (29.4%). Mixed lesions were present in 85 of 119 cases (71.4%). Successful maturation defined by fistula use was achieved in 99 of 119 cases (83.2%). Numerous other articles describe similar results of various percutaneous interventions to aid in fistula maturation. It is important to emphasize that the majority of articles reporting treatment for nonmaturing AVF use a variety of interventions, often of multiple types and sequentially over time, making it very difficult to ascertain the role of each intervention. In particular, accessory or competing vein branch obliteration has been incorporated into the interventional maturation strategy in several reports but typically in combination with angioplasty, making it very difficult to draw confident conclusions about this particular intervention.

Treatment of discrete stenosis with percutaneous angioplasty is the most readily apparent intervention that would be expected to enhance fistula flow and contribute to successful maturation. Treatment of a variety of lesion types and sites has been reported. Falk reported 66 venous angioplasties and 16 arterial angioplasties among 113 interventions performed. Beathard and colleagues reported venous stenosis in 78% of cases, with 43% involving the juxta-anastomotic fistula segment. Treatment of a typical juxta-anastomotic stenosis is demonstrated in Figure 3. Stenosis involved the arterial anastomosis in 38% of cases, all
associated with juxta-anastomotic lesions. Stenosis occurred in the artery separate from the anastomosis in only 4% of cases. Some of these distinctions are clouded by the lack of a uniform definition among reports as to what constitutes arterial angioplasty in the setting of native AVF. In any case, these and other studies clearly demonstrate a wide variety of discrete stenotic lesions affecting any and all segments of the access circuit from the feeding artery through the central veins. Asif and colleagues reported the results of 112 percutaneous angioplasty procedures for treatment of stenosis restricted to the perianastomotic fistula segment in 73 consecutive patients. In this relatively homogeneous group, procedure success was 97%; primary patency at 6 and 12 months was 75% and 51%, respectively; and secondary patency at 6 and 12 months was 94% and 90%, respectively.

The term balloon maturation has not been rigorously or uniformly defined. Miller and colleagues recently reported the results of fistula maturation using a variety of interventional techniques, including “aggressive staged balloon assisted maturation” for deep and/or small-caliber fistulae. This technique involves dilation of the entire fistula tract using long angioplasty balloons. Initially, 6 to 8 mm balloons were used, with sequential procedures at 3-week intervals, each time increasing balloon size by 2 to 3 mm up to a maximum of 16 mm. This technique was combined with other interventions, including ligation or coil embolization of competing vein branches. Furthermore, this study divided patients into two subgroups: those who met NKF-KDOQI criteria for maturity based on size, flow, and depth were categorized as class 1 fistulae. Those who did not meet the NKF-KDOQI criteria based on small size (2–5 mm diameter) or excessive depth (≥ 6 mm) were categorized as class 2 fistulae. This study showed successful fistula maturation in 118 of 122 patients using these techniques. Class 1 patients required fewer procedures (1.6 vs 2.6) and shorter periods of time (5 vs 7 weeks) to achieve maturation compared to class 2 patients. Primary and secondary patencies for class 1 and class 2 patients, respectively, were reported to be 17% and 39% at 6 months; 72% and 77% at 12 months; 53% and 61% at 24 months; and 42% and 32% at 36 months. These differences were not shown to be significant, and secondary patencies were comparable to those reported in other studies. The principal importance of this article is the description of the rather novel method of dilating veins without discrete stenosis using sequentially larger balloons (ie, balloon maturation) to enhance and/or accelerate their suitability for dialysis needle access.

Accessory or competing vein obliteration by ligation or coil embolization has been included in multiple reports previously mentioned that describe responses to interventions and outcomes in immature fistulae. Figure 4 illustrates a typical accessory vein ligation procedure. In most reports, vein obliteration was combined with other percutaneous interventions to treat stenosis, making it difficult to demonstrate the benefits and outcomes attributable to vein obliteration alone. One series reported fistula maturation outcomes following percutaneous obliteration of accessory veins, without the presence of stenosis or use of angioplasty. In this report, 17 patients underwent accessory vein obliteration using a percutaneous suture method; one to three accessory veins were ligated in each case (mean 1.7). This resulted in successful fistula maturation in 15 patients (88%) by 1.7 months (range 0.3–6 months) postintervention. Lack of a uniform, verifiable definition of clinically significant competing veins constitutes a major limitation in all reports of vein obliteration. This has been based largely on the operator’s subjective interpretation of the physical examination, size of the vessels, and angiographic appearance of flow. Distinguishing between detrimental competing veins,
inconsequential accessory veins, and beneficial collateral veins is crucial but not well elaborated in any trials. Collateral veins that develop in response to outflow stenosis must not be treated with vein obliteration techniques unless they are deemed to be diverting significant flow away from the fistula after definitive correction of the outflow stenosis. No study to date has quantitated fistula flow or pressure in the primary vein and the accessory vein before and after vein obliteration. Such measurements would be necessary to convincingly demonstrate the hemodynamic benefits of eliminating competing veins. Furthermore, some have argued for preservation of any or all accessory veins as potential vessels for cannulation sites or material for subsequent surgical revision. It is possible that premature loss of these veins may be detrimental to long-term fistula outcomes.

Early fistula thrombosis is the most extreme case of maturation failure. There is ample evidence that thrombosis of functional native fistulae can be successfully treated using percutaneous methods. These results may not be applicable when a native fistula thromboses in the early postoperative period, before there has been an opportunity for vessel remodeling to occur, and before the fistula has been deemed suitable for hemodialysis needle access. There are no published data detailing the outcomes of surgical or percutaneous interventions to treat thrombosed immature native fistulae. Several of the reports referred to previously did include patients with early fistula thrombosis, but these cases were not described or analyzed separately and no conclusions can be drawn regarding outcomes in this subgroup. In the absence of such data, one would expect such cases to be technically challenging, with relatively poor technical success and long-term outcomes versus thrombectomy of functional fistulae. The decision whether or not to attempt percutaneous thrombectomy to salvage thrombosed immature native AVF must therefore depend on the judgment of the operator. The most important considerations are the prethrombosis examination of the fistula, the duration of thrombosis, and the profile of the thrombosed vein on physical examination. If the operator is confident that the prethrombosis fistula examination was relatively favorable, the duration of thrombosis short, and the thrombosed vein relatively soft, superficial, and easily palpated, then attempted thrombectomy may be in order. Conversely, if the prethrombosis physical examination was unpromising, the duration of thrombosis relatively long, and the vein palpable as a hard thin cord, then attempted thrombectomy is probably futile. Further study is needed to elucidate the factors that favor successful thrombectomy in this setting.

Often neglected in the assessment of fistula maturation, interventions, and outcomes is the issue of “quality.” Even looking at functional, mature AVF, there is a large gap between a high-quality and a low-quality AVF. After repeated interventions, the patient may still be left with a fistula of marginal quality, difficult or unpleasant to cannulate, barely able to sustain adequate dialysis therapy, and destined to require frequent repeated interventions. At what price does fistula maturation strategy succeed? In such cases, we may not have done the patients a good service or provided them with an access superior to a well-constructed nonautogenous graft as measured by the frequency of
interventions, patient comfort and satisfaction, primary and secondary patencies, or adequacy of hemodialysis.

No discussion of fistula maturation would be complete without reference to needle access technique. Whatever the perceived quality of the fistula, response to interventions, size and depth of the vein, or fistula blood flow, ultimately, the true test of maturity is whether it can be safely, reliably, and repeatedly accessed using suitably sized dialysis needles. As with any technical skill, there is considerable variability in the experience and ability of dialysis technicians or nurses involved in fistula cannulation. Some programs and providers are highly skilled in the use of buttonhole needle access, which may be essential for successful cannulation of certain fistulae. Substantial variability exists from program to program and even among the staff within a given program. Thus, it is incumbent on all programs and health care professionals to work toward improving fistula assessment and cannulation skills. It is also important to develop systems to ensure that those providers with the highest level of technical skill are used to cannulate the most challenging fistulae. All efforts to advance fistula maturation and use will surely be confounded by poor cannulation technique with attendant vessel injury, infiltration, hematoma, aneurysm, or pseudoaneurysm formation. In the process, the patient will pay the price with unpleasant, painful, or prolonged dialysis sessions and inadequate hemodialysis. Under such circumstances, patients may not appreciate the potential long-term advantages of a native AVF in the face of their own very immediate negative experiences. For some patients, this may result in “fistula phobia,” refusal to accept further surgical or interventional procedures, and, ultimately, long-term catheter dependence.

Finally, there are special considerations applicable to angiographic evaluation and intervention for immature fistulae in patients with advanced-stage chronic kidney disease who are not yet receiving hemodialysis treatment. Surgical fistula construction is recommended at least 6 months prior to the anticipated need for hemodialysis to allow sufficient time for maturation. For all the reasons discussed above, these fistulae may fail to mature. Concerns about exposure to iodinated contrast media and risks for acute kidney injury may discourage some interventional physicians from performing necessary imaging studies. Carbon dioxide can be used in such cases and may provide sufficient image quality to guide intervention. However, carbon dioxide is an inherently limited imaging modality that provides less effective contrast and incomplete anatomic information compared to imaging with iodinated contrast media. Furthermore, carbon dioxide imaging of the upper extremity arterial system is not advisable owing to the risk of retrograde passage of carbon dioxide bubbles into the central arterial circulation. Asif and colleagues reported the use of low-dose iodinated contrast (10–20 mL) for venographic imaging in 25 patients with stage IV or V chronic kidney disease. No cases of acute kidney injury were observed. Kian and colleagues reported the results of 65 imaging studies in 34 patients with stage IV chronic kidney disease and an immature fistula who received low-dose iodinated contrast (mean dose 7.8 mL). Mild acute kidney injury was observed in 4.6% of studies, all spontaneously recovering to baseline without requirement for acute dialysis or other adverse clinical sequelae. Therefore, it is recommended that immature fistulae in chronic kidney disease patients be judiciously studied and intervened on as necessary to achieve functional maturation prior to the need for hemodialysis therapy.

In conjunction with the End Stage Renal Disease Network 4 Medical Review Board, our practice has developed an algorithm to ensure timely assessments of developing fistulae and facilitate interventions required to achieve functional maturation (Figure 5). This provides a framework for tracking fistula maturation based on suitability for needle access and ability to deliver adequate blood flow.

**Conclusion**

Many autogenous AVF fail to mature spontaneously after surgical construction owing to a variety of anatomic and hemodynamic factors. The determination of whether a fistula is mature depends not only on physical factors such as vein size, vein depth, and blood flow but also on individual patient requirements for hemodialysis clearance. A large percentage of immature fistulae can be salvaged by appropriate use of minimally invasive and surgical techniques. Timely assessment and interventions are necessary to achieve the best possible fistula outcomes. Early abandonment and construction of new arteriovenous access may be warranted in the setting of a low-quality fistula with unfavorable anatomy or poor responses to percutaneous interventions.

**Acknowledgment**

Dr. Saad is a consultant and clinical investigator for Bard Peripheral Vascular as well as a consultant for W.L. Gore & Associates.

Financial disclosure of reviewers: None reported.
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Figure 5. Fistula maturation protocol.