13 Approach to a Patient with Non-maturing AV Fistula

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Introduction

The superiority of the native arteriovenous fistula (AVF) over other types of accesses including arteriovenous graft (AVG) and tunneled dialysis catheters (TDC) for chronic hemodialysis (HD) is well-recognized. AVF has been shown to have superior patency rate and lower complication rate including a low risk of infection and a lower intervention rate to maintain its patency [1, 2]. This is the fundamental reason underlying various vascular access guidelines and the Fistula First project in the United States that led to predominantly AVF creation in the majority of patients with end-stage kidney disease (ESKD).

AVF maturation failure rates remain high. The most recent annual data report of the United States Renal Data System (USRDS) demonstrated that 39% of AVFs placed between 2014 and 2016 failed to mature sufficiently to use for dialysis [3]. Older reports had similar findings with ranges between 28% and 53% [4–7]. Failure to mature (FTM) often commits these patients to a TDC for a variable length of time until they have a well-functioning arteriovenous (AV) access [4]. In addition to the risk of infection and central venous stenosis, the catheters also contribute to inadequate dialysis and poor patient outcomes [4]. Therefore, early recognition and timely intervention in case of an AVF with FTM is critically important [4].

Failure to Mature (FTM): Definition

Fistula failure can be classified as early and late. Early or primary failure is a true FTM that refers to the cases in which the AVF never develops to the point where it can be used, or fails within the first 3 months of usage [1]. Late or secondary failure refers to those cases where the AVF fails after a period of successful usage [8, 9]. Although there might be considerable overlap in the causes of both early and late failure, early failure has gained significant attention as data have demonstrated that a great majority of the failed AVF can be salvaged using percutaneous interventions [10–13]. While it is not infrequent to abandon these AVFs with early failure, aggressive evaluation and treatment have been shown to result in salvage of a vast majority of these accesses [11].

Risk Factors for Failure of Maturation

As mentioned above, FTM remains a common problem occurring in 28–53% of native AVFs [3–7, 14, 15]. Several studies have looked at factors that might predict AVF maturation.

Preoperative vascular mapping has been shown to improve the rate of AVF placement and overall surgical success rate [16–18]. Creation of AVF using very small arteries (e.g., <1.6 mm in diameter) and veins is likely to fail, although the precise cutoff hinges on the available surgical experience and expertise [16].

Perhaps the most critical determinant of AVF maturation is the functional ability of the artery and vein to dilate and achieve a rapid increase in blood flow after surgery [16]. Several studies have shown that postoperative flow rate measured by Doppler ultrasound in a forearm fistula is a moderately good predictor of fistula maturation [19, 20]. In addition, these studies have reported using a cutoff between 400 and 500 ml/min at 2–8 weeks as a predictor of fistula maturation. Clinical examination of the fistula may be as accurate as Doppler flow measurement [19–21]. Other predictors of AVF failure include age >65 years, diabetes mellitus, female gender, and high body mass index (>27). However, angiographically detected anatomic abnormalities are present in the majority of the patients with early FTM [1].

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Causes of Early Fistula Failure

AVF maturation failure can be classified into three major categories:

1. Inflow problems: poor arterial inflow and juxta-anastomotic stenosis (JAS).
2. Outflow problems: failure for the vein to "arterialize" and the presence of large and/or multiple accessory veins.
3. Other technical factors related to surgical procedure: e.g., a deep fistula, although mature, might not be easily accessible for cannulation and may require transposition in order to support dialysis adequately.

Majority of these causes can, and must be, identified early in order to salvage the AVF.

Inflow Problems

A good inflow is critical for fistula maturation and for attaining adequate flow rates to deliver dialysis. After AVF creation, the arterial flow is expected to increase, with gradual increase in arterial diameter and changes in flow pattern [16]. Vascular remodeling and dilation are typically attained as a result of longitudinal shear stress and circumferential deformation, in the milieu of vasoactive factors [16, 22]. This process may continue over a long period of time and contributes to maturation. Rarely, a small-size artery or presence of arterial disease such as atherosclerosis can result in early fistula failure. However, this can be identified and prevented by a comprehensive patient evaluation prior to access placement.

JAS is one of the most common causes of maturation failure in angiographically evaluated AVFs and is mostly present in the vein adjacent to the anastomosis, though it can sometimes also affect the adjacent artery [17] (Fig. 13.1). Although precise etiology is not clear, it is postulated that the JAS occurs in the swing segment of the vein, where the vein is mobilized to connect with the artery and suffers stretching, torsion, and spasm [23]. It is unclear as to what extent these factors contribute to JAS; however, the net effect of JAS is to reduce AVF inflow. JAS often occurs early in the process and often results in early access failure.

In one single-center retrospective study, the authors reported their 12-year experience of radiological management of stenosis and thrombosis in both AVF and AVG [24]. Of the total 283 patients with AVF, 74% (209) had a forearm AVF, and 26% (74) had upper arm AVF. In patients with forearm AVF, JAS was present in almost half leading to an inflow problem (Fig. 13.2a). However, of the 74 patients with the upper arm AVF, outflow venous stenosis was predominantly reported in 55% (n = 41) (Fig. 13.2b). The vast majority of the stenoses (86%) were less than 2 cm long [24]. In another more recent single center prospective study of 246 patients over 7 years a larger AVF diameter and higher blood flow measured by ultrasound within 90 days of AVF creation were associated with a higher probability of unassisted maturation [15].

Fortunately, JAS is amenable to treatment by percutaneous angioplasty or surgery [1, 11, 25]. A retrospective analysis of prospectively collected data compared outcomes and cost of surgery (n = 21) and percutaneous transluminal angioplasty (PTA) (n = 43) for JAS in a total of 64 patients [26]. Although the results showed similar cost and success rate, adjusted relative risk was 2.77 for restenosis within the PTA group. The primary 1-year unassisted patency rate for surgery was 91 ± 6% as compared with 54 ± 8% with PTA, although adjusted-assisted primary patency rates were similar in the two groups. The surgical approach had the advantage of less restenosis but was more invasive, involved small but significant risk of loss of venous capital, and was associated with a higher median cost, primarily because of the procedure-related hospitalization. It is important to note that the study was not randomized and only included patients with mature AVF based on the choice made based on available expertise and technical facilities as suggested by the authors. It is worth reemphasizing that JAS can be easily diagnosed by physical examination [27, 28].

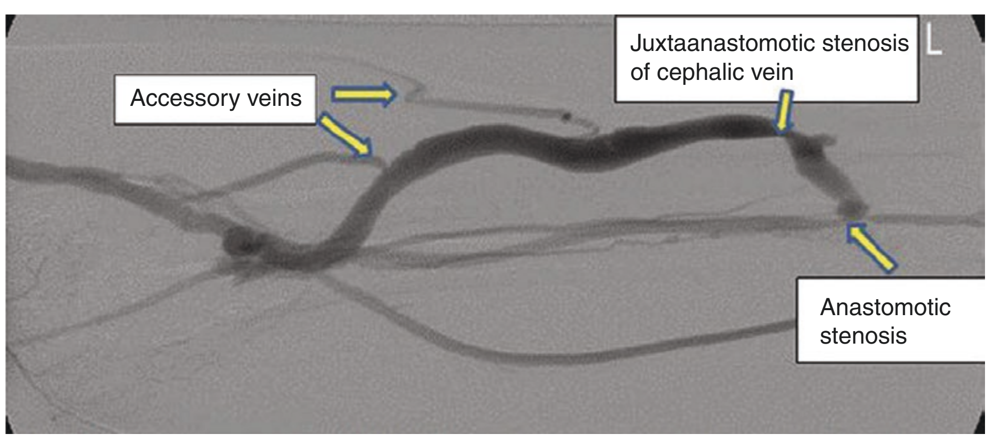

Fig. 13.1 Fistulogram of radiocephalic AVF showing arteriovenous anastomotic stenosis and juxta-anastomotic stenosis of cephalic vein and accessory veins in the forearm

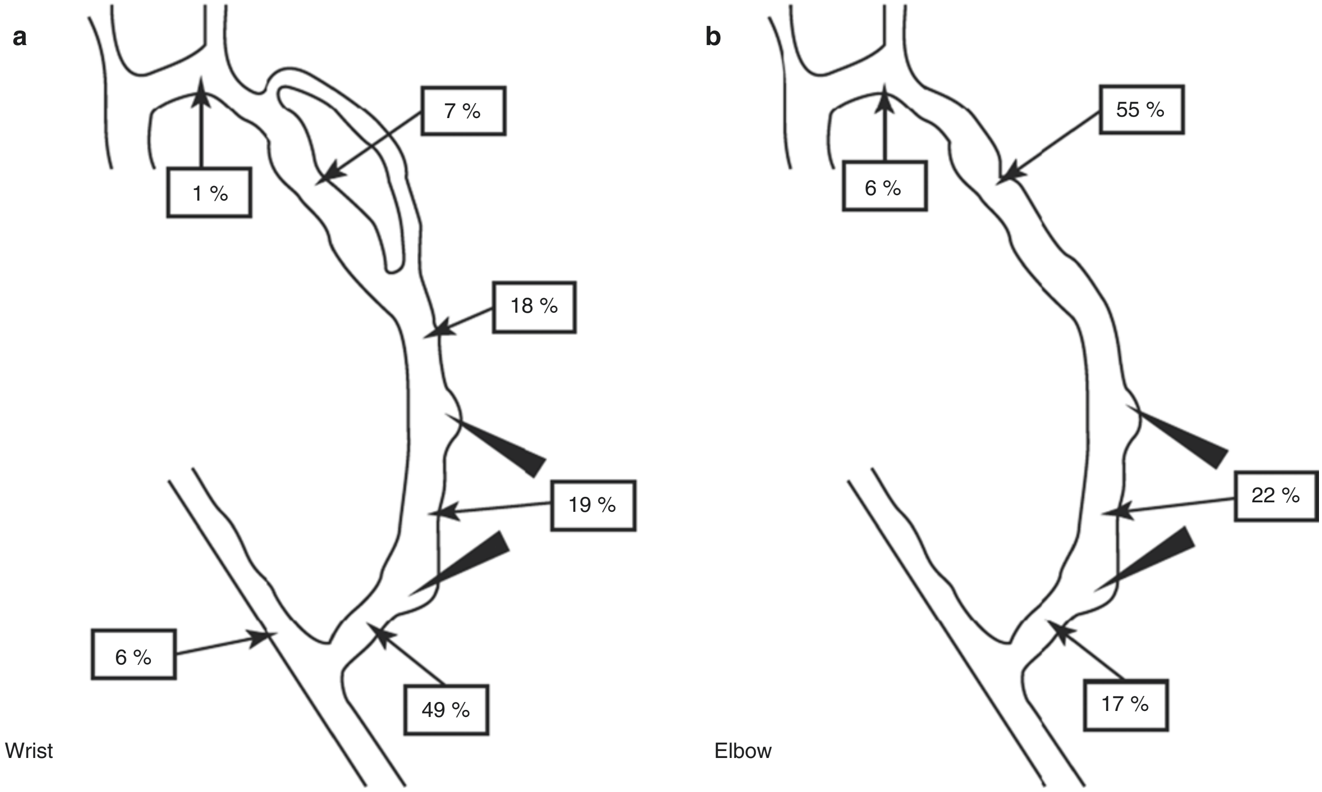

Fig. 13.2 (**a**, **b**) Common sites of stenosis in AVF. (**a**) In wrist AVF. (**b**) In upper arm AVF. (Reproduced with permission from Turmel-Rodrigues et al. [24])

Outflow Problems

After AVF creation, venous dilatation ensues, initially as a result of increased venous pressure and later because of the increase in flow-mediated shear stress [16, 17]. For an AVF to mature enough and be used to provide satisfactory HD, there must also be sufficient blood flow through the outflow vein. The absence of good outflow will result in failure of the access. Anomalies that lead to outflow problems include veins that are too small for AVF development, veins that are fibrotic or stenotic, or presence of side branches, referred to as accessory veins. Failure of the dilation of the outflow vein has been suggested to be a common cause of maturation failure [29].

Venous stenosis is the cause of failure of the majority of AVF. Endovascular techniques have become popular in the treatment of most venous stenoses (Fig. 13.3a, b). However, recurrent lesions remain problematic, especially with a long segment of severely narrow lesions [30]. Close surveillance and repeated interventions are generally required to maintain patency, although the restenosis at 6 months is significantly less with AVF, compared with AVG [31].

Although a single cephalic vein stretching from the wrist to the antecubital space is ideal, in many cases, it may be accompanied by one or more accessory veins [27]. Accessory veins are part of normal anatomy. All veins receiving the flow from the newly created anastomosis enlarge after creation of AVF, and a small accessory vein may also become enlarged with time. The accessory veins must be distinguished from the collateral veins which are pathological and are associated with a downstream (antegrade) stenosis. Ideally, the presence of an accessory vein may be viewed as an advantage since it might provide an additional venous channel suitable for cannulation. However, when large (>25% of the diameter of main AVF), the accessory vein can steal enough blood flow so that the main fistula channel does not dilate, often resulting in early AVF failure [27, 32] (Fig. 13.4). The accessory veins can often be diagnosed by physical examination [33, 34]. Frequently they are visible or can be detected by palpating the fistula. Also, the thrill that is palpable over the arterial anastomosis usually disappears when the downstream (antegrade) fistula is manually occluded, but it does not disappear if an outflow channel (accessory vein) is present below the point of occlusion [28] (Fig. 13.5). In an immature AVF, ligation or coiling of these accessory veins will redirect the flow to the main channel and promote the development of a usable AVF [1, 11]. Accessory veins

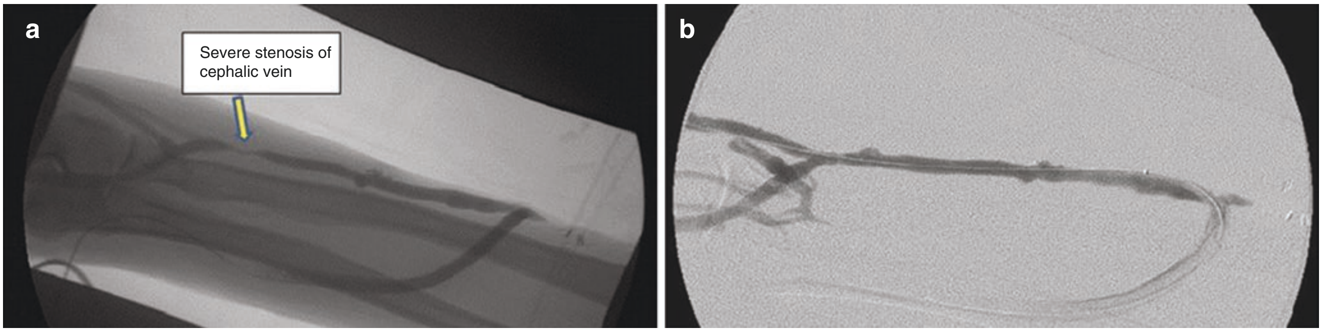

Fig. 13.3 (**a**) Cephalic vein in forearm with severe stenosis that can be angioplastied for maturation of AVF. (**b**) Cephalic vein in forearm after angioplasty leading to maturation of AVF

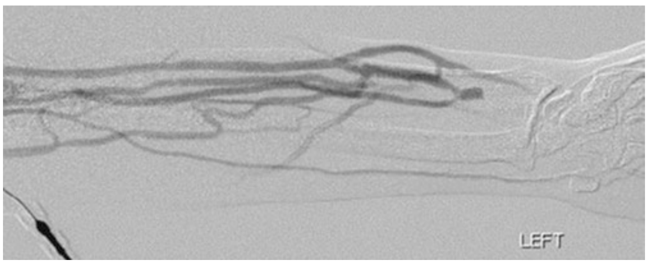

Fig. 13.4 Fistulogram of forearm radiocephalic AVF showing multiple large accessory veins

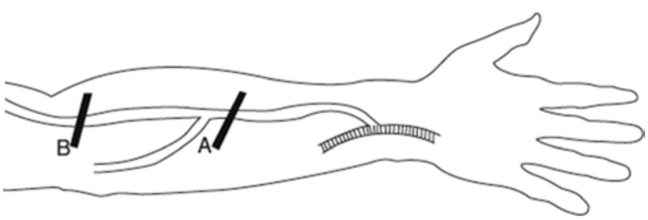

Fig. 13.5 Physical examination of accessory vein. When the fistula is occluded at *point A*, the thrill will disappear at the anastomosis. As the point of occlusion is moved upward past the accessory vein to *point B*, the thrill will continue when the fistula is occluded. (Reproduced with permission from Beathard [27])

together with the JAS represent the two most common causes of early AVF failure [35, 36]. These two lesions are often present simultaneously [24, 37].

With the introduction of endovascular AVF (endo-AVF) creation, accessory vein ligation may become more common. While endovascular AVF creation in general requires less postoperative interventions, accessory vein obliteration is one of the interventions that is more commonly required. In a study of 32 patients who underwent endo-AVF creation using WavelinQ EndoAVF system, 28% of the patients required coiling of accessory veins [38]. In other studies that compared the rate of interventions in endo-AVF patients versus traditional surgical AVF, the rate of accessory vein ligation per patient-year was 0.207 vs 0.007 in one study [39] and 0.143 vs 0.100 in another [40].

Identification and Management of Early *AVF Failure*

Identification of patients who are at risk of early AVF failure is critical in order to perform timely intervention to salvage the AVF [1, 17]. Physical examination of the AV access is not only easy to perform and inexpensive; it also provides a high level of accuracy [27, 41]. Both stenosis and accessory veins, along with JAS, can be easily identified by a thorough physical examination of the AV access [8]. Point of care ultrasonography (POCUS) can be utilized in addition to physical exam to provide a more comprehensive evaluation. Please refer to the chap. 12 ("Approach to Arteriovenous Access") for details regarding access examination. While detailed traditional ultrasonography can identify these lesions successfully, it may not be readily available in all centers and is not free of added cost.

Given the fact that there is very little change in the AVF blood flow or diameter after the first month along with the finding that AVF maturation can be judged with high accuracy via physical examination, it is recommended that all newly created AVFs should be evaluated by an experienced examiner at 4 weeks [1, 11, 42, 43]. An angiographic study must be performed for non-maturing or poorly mature AVF [4]. In patients who have not initiated dialysis, there is often a concern with the use of radiocontrast. However, a small amount of contrast use has been shown to be safe in the evaluation of AVF [44].

An early identification and intervention approach is critical for two reasons. First, a majority of AVFs with early failure demonstrate stenotic lesions within the access circuit, and vascular stenosis is a progressive process eventually culminating in access thrombosis, with the risk of permanent loss of the access [1, 11, 12]. Failure to act promptly in these AVFs will result in a loss of the opportunity to salvage an AVF. Second, patients with early AVF failure are often committed to a TDC exposing them to all the dreaded complications of catheter use. Hence, early intervention to identify and salvage early AVF failure becomes an important part of preventing AVF loss and minimizing complications related to catheters. Such an approach also supports the "catheter last" approach that the experts advocate.

Specific Interventions

Once a patient with early AVF failure has been identified, appropriate action to salvage the AVF should be taken in a timely manner. As previously mentioned, studies have demonstrated that the two most common problems observed in early AVF failure are the presence of stenosis and accessory veins [10–12]. Fortunately, a great majority of these failed AVFs can be salvaged using percutaneous techniques [1, 12, 45].

Angioplasty

Endovascular intervention to salvage an immature or failing AVF has become routine. Using radiocontrast, an angiogram of the AVF (commonly termed as "fistulogram") is done to diagnose the presence of anatomic abnormalities, which can usually be treated with percutaneous transluminal angioplasty (PTA). PTA is typically indicated when there is >50% stenosis of AVF or AVG [17, 34]. An inflow lesion, if identified, may be amenable to PTA via a retrograde approach. In a prospective observational study, 100 patients with early FTM underwent evaluation and treatment at 6 freestanding outpatient vascular access centers [1]. Vascular stenosis and presence of a significant accessory vein alone or in combination were found to be the most common offenders. Venous stenosis was present in 78% of the cases. A majority (48%) of these lesions were found to be close to the anastomosis (JAS). A significant accessory vein was present in 46% of the cases. PTA and accessory vein obliteration using one of the three techniques (percutaneous ligation using 3/0 nylon, venous cut down, or coil insertion) were used to salvage the failed AVF. Angioplasty was performed with a 98% success rate, and there was 100% success rate for accessory vein ligation. These interventions resulted in dialysis initiation using the AVF in 92% of the cases [1]. Upon further analysis, 84% of the AVFs were functional at 3 months, 72% at 6 months, and 68% at 12 months [1]. The overall complication rate in this series was 4%, exclusively seen in patients who underwent angioplasty. Of these, only one patient (1%) had a major complication consisting of a vein rupture with an expanding hematoma resulting in loss of the access. The three minor complications included low-grade hematomas requiring no treatment and no sequelae [1].

Accessory/Branching Vein Ligation

Ligation of the accessory veins can be performed surgically or percutaneously with suture ligation and/or embolization. Suture ligation is useful in patients with superficial accessory veins given minimal distance for subcutaneous dissection [46]. Coils within superficial veins can be irritating to patients and possibly erode through the skin. However, coil embolization is preferred in those with deep accessory veins as cutdown suture ligation is more difficult with potential risks of nerve/muscle and tendon injury [46]. Using a percutaneous ligation technique, a separate report also described accessory vein ligation of fistulas that failed to achieve adequate blood flow or size for successful cannulation. Authors reported that of the 17 AV fistulas, 15 (88%) successfully matured at 1.7 months (±1 month) after the procedure and were functioning at 44.5 (±12 weeks) after the first use [10].

In another series of 119 patients with AVF complicated by maturation failure, 29.4% had a significant accessory vein but that was the sole cause of AVF dysfunction in only 3.4% [45]. The AVF salvage rate for all lesions was 83% in this series. These reports suggest that early intervention for maturation failure can salvage a majority of AVF using endovascular techniques [1, 12, 17].

Sequential Dilation

Occasionally early fistula failure is found due to a long segment of the vein which is diffusely small or stenosed. Recent reports have highlighted a newer technique (sequential dilatation or balloon-assisted maturation) to salvage an AVF that fails to develop because of diffuse stenosis [6, 47]. In this technique, the AVF is gradually dilated with a progressively increasing size of angioplasty balloon at 2- to 4-week intervals until a size that is optimal for dialysis cannulation is achieved. The goal is to progressively dilate the outflow vein to a point that it is usable for repetitive cannulation and will also deliver adequate blood flow. Dilation time is typically <20 s mainly to reduce the chance of thrombosis [46]. In addition, shutting down or occluding flow to the AVF by compressing the anastomosis during vein dilation is recommended to prevent venous tears resulting in blood leaking out subsequently causing ecchymosis [46]. Balloon dilatation is usually performed starting from the central to the peripheral vein to reduce the likelihood of blood extravasation as it is easier to pull back a balloon than push it forward [46].

Surgical Techniques

Surgical interventions include patch angioplasty, creation of a combination of fistula and graft ("graftula"), creation of a new anastomosis for a juxta-anastomotic lesion, and superficialization procedures [4, 46]. However, large-scale randomized prospective studies examining the role of surgical approach in the salvage of AVF with early failure are lacking. Inability to navigate the wire across a stenotic lesion during percutaneous approach and deep location of an AVF are some of the indications for surgical intervention [4].

Stents in AV Access

Stents have a very limited role in salvaging immature AVFs. When dealing with the stenosis, patients with >30% residual stenosis after PTA of venous stenosis or those with recurrence of the stenosis within 3 months and requiring repeated intervention should be considered for a stent placement [17]. Stents can also be useful in the case of vessel rupture during angioplasty that does not respond to conservative measures. The latter, however, is generally associated with poor primary patency [48]. Stents can also be used when PTA has failed and surgery is not feasible due to a variety of reasons.

Although stents have been used in coronary and peripheral arterial circulation with decent success, dialysis access demonstrates unique pathologies with the outflow being part of venous circulation. Self-expanding rather than balloon-expanded stents are commonly used for VA [49]. These include bare metal stainless steel stents or nitinol shape memory alloy recoverable technology (SMART) stents that are made of nickel-titanium alloy [17]. These have physical characteristics that allow more deformability as compared with bare-metal stents.

Stent grafts are composed of nitinol skeleton covered by graft material on both sides. Stents available until recently have been used off-label to improve patency in patients with VA stenosis, primarily in AVG, with variable results. Stent placement has several disadvantages including migration, fracture, and in-stent restenosis [17]. Infectious complications are usually not evident until many days after the procedure [50]. Additionally, due to the stent placed in the venous segment, loss of vein length may jeopardize cannulation length and future AVF creation [17]. Despite the recent advances in knowledge, both technical and theoretical, the role of stent placement in the management of hemodialysis access dysfunction remains controversial. It will remain so until large, multicenter, prospective, randomized, controlled trials are conducted [50].

Stent placement should be utilized only after considering the type, location, and frequency of recurrence of the lesion. Possibility of a secondary AVF must be considered to avoid the loss of available venous length from stent placement.

Thrombectomy

If the immature AVF is thrombosed, then one can perform a thrombectomy (sometimes also referred to as declotting) with simple PTA maceration of the clot in most cases [6]. There is typically a minimal amount of thrombus usually located in the juxta-anastomotic region. Anticoagulation with heparin is generally indicated. The treatment should also include prompt detection and treatment of the underlying anatomic abnormality and evaluation and management of outflow, including central veins, to avoid rethrombosis. Percutaneous thrombectomy of AVF is more difficult than thrombectomy of AVG, with success rates that vary between 73 and 96% in the published literature [51]. With the advent of new technology and growing expertise in the field of interventional nephrology, the results of percutaneous techniques have improved significantly and are now comparable to surgical thrombectomy with restoring AVF patency in >90% of cases [52–54]. However, the results seem to vary with operator experience and available resources.

Prevention of Early FTM

Appropriate preoperative evaluation of the patients prior to AVF creation will not only increase chances of AVF creation but also of AVF maturation. Use of physical examination, ultrasonography, and occasional venography are recommended based on individual case. Although the use of certain pharmacologic agents, especially the antiplatelet agents, has been noted to be associated with improved survival of AVF, it has not been proven conclusively to improve the use of AVF in randomized controlled trials despite reduction in AVF thrombosis [55–58]. Many novel therapies are being evaluated to improve maturation of AVF. Local delivery of endothelial cells as a wrap can reduce development of neointimal hyperplasia at the arteriovenous anastomosis [59]. Perivascular wraps of antiproliferative agents (paclitaxel) and gene therapy with adenoviral vectors have been tried [60]. Use of venous and arterial allografts as well as decellularized xenografts have been tried in those with unsuitable veins. Better hemodynamics by way of using a premade arteriovenous anastomosis have also been tried in clinical studies. Vein preconditioning throught a gradual increase in blood flow through the cephalic vein using an external pump is also being tested [61].

Conclusion

It is crucial to evaluate a newly created AVF at 4–6 weeks after placement to identify candidates with early AVF failure. Physical examination is a simple but efficient modality of identifying such candidates. Once identified, these patients should be referred to an interventionalist for evaluation and appropriate intervention. Delays in such intervention may result in the delivery of dialysis with a catheter rendering the patient susceptible to higher complications as well as to a risk of eventual thrombosis leading to permanent loss of access. Use of the percutaneous endovascular techniques such as balloon angioplasty and vein obliteration can rescue the majority of early AVF failures.

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