

Hemodialysis access thrombosis

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Abstract: For the over 400,000 patients in the United States dependent on hemodialysis, arteriovenous (AV) access thrombosis may lead to missed dialysis sessions, inpatient admissions and the need for placement of temporary dialysis catheters. It is also the leading cause of permanent access loss. Percutaneous declotting is generally preferred over surgical thrombectomy. Various percutaneous approaches can be employed including the lyse-and-wait technique, thromboaspiration, pulse spray aided pharmacomechanical thrombolysis, and use of mechanical thrombectomy device.

Keywords: Arteriovenous fistula (AVF); arteriovenous graft (AVG); AV access thrombosis; pulse spray aided pharmacomechanical thrombolysis

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Introduction

Approximately 430,000 patients in the United States are dependent on hemodialysis (HD) (1). Options for HD access include catheters, arteriovenous grafts (AVGs) and arteriovenous fistulas (AVFs). AVG thrombosis occurs approximately 0.5–2.0 times per year and AVF thrombosis occurs 0.1 to 0.5 times per year (2). AV access thrombosis occasionally leads to multiple missed dialysis sessions, inpatient admission and placement of a temporary dialysis catheter. Access thrombosis accounts for 65–85% of cases of permanent access loss (2). After considering potential contraindications, endovascular declot should be performed. Various approaches include pulse spray aided pharmacomechanical thrombolysis, mechanical clot maceration and the lyse-and-wait technique (3–5).

Monitoring and surveillance

Monitoring and surveillance are employed in order to identify a dialysis access at risk of thrombosis with the goal

of intervening before thrombosis occurs (6,7). The efficacy of monitoring and surveillance in preventing access thrombosis and prolonging the life of the access is uncertain (8,9).

Monitoring consists of focused physical examination of the access and review of data gathered during the normal course of dialysis such as Kt/V, serum potassium, pump pressures and problems with access cannulation (e.g., prolonged bleeding after needle removal) (6). Physical examination, performed at least monthly by a qualified practitioner, includes looking at, feeling and listening to the access to identify possible stenoses that place the access at risk of thrombosis. Signs of outflow stenosis include development of aneurysmal dilation of the access, abnormally increased pulsatility, a discontinuous thrill and a high-pitched bruit in the outflow vein. Signs of inflow stenosis include a flat fistula, poor turgor or a weak bruit (10). Kt/V quantifies dialysis adequacy. K represents the clearance of urea, t represents the dialysis time and V represents the volume of distribution of urea. Low Kt/V denotes inadequate dialysis, which adversely affects the patient's quality of life and is associated with lower

survival (11). A low Kt/V may indicate poor access flow which places the access at risk for subsequent thrombosis (12). A Kt/V of <1.2 or an interval decrease by more than 0.20 should prompt intervention both to increase dialysis adequacy as well as forestall potential access thrombosis (13). Prolonged bleeding after needle withdrawal is a common sign of outflow stenosis. Excessively negative pre-pump arterial pressure is a sign of inflow stenosis.

Surveillance is the periodic employment of specialized instrument based testing. Examples include access flow measurements (Q_a), static venous pressure measurements, quantification of recirculation and Duplex ultrasound (6).

Access flow measurement is the most reliable and validated surveillance tool (14). AVGs are at risk of thrombosis when Q_a falls below 500 mL/min. AVFs are at risk of thrombosis when Q_a is less than 300 mL/min. The main reason AVGs thrombose at higher flow rates than AVFs is that they lack an endothelium (15). Falling Q_a is highly predictive of subsequent access thrombosis; one study showed a near 14-fold increase in access thrombosis when Q_a dropped to 65% of baseline (16).

Static venous pressure measurements are useful in AVGs where the site of stenosis predictably occurs just downstream from the graft-to-vein anastomosis. Static venous pressure measurements in AVFs are of lower utility in predicting access thrombosis for multiple reasons. For one, AVFs often have stenosis involving the inflow. Additionally collateral vessels may develop and enlarge, dissipating the increased intra-access pressures in the setting of outflow stenosis. An access to systemic pressure ratio less than 0.4 is normal; a ratio greater than 0.5 should trigger evaluation (17).

Recirculation occurs when blood that has just been through the dialysis machine returns back into the dialysis machine rather than flowing towards the right atrium. This can occur with both with inflow and outflow stenoses. By definition recirculation can only occur when Q_a is less than pump flow rate (Q_b). When recirculation is due to outflow stenosis, it occurs because the path of least resistance is retrograde, through the AV access (i.e., towards the feeding artery) and into the arterial needle, rather than antegrade (i.e., through the outflow stenosis). When recirculation occurs secondary to inflow stenosis it is because the inflow is unable to support the amount of flow required to maintain the set Q_b ; the arterial needle has to “borrow” blood returning into the access via the venous needle

to maintain the flow rate demanded by the pump (13). Recirculation is an ineffective surveillance technique. First, it is only an indirect measure of Q_a , which can be measured more precisely by other methods. Second, it is insensitive in identifying an AVG at risk of thrombosis. This because Q_b is typically set at 300 mL/min and recirculation will only occur when Q_a is less than this set Q_b . An AVG is at risk of thrombosis when flow rates are less than 500 mL/min. Additionally, stenosis between the two needles cannot be detected by measuring recirculation. Finally, recirculation can occur when there is accidental needle reversal, making it a non-specific finding.

Ultrasound can be used as a surveillance tool. A $>50\%$ stenosis is likely when there is a focally elevated peak systolic velocity of >400 cm/s or a local peak systolic velocity ratio of >2.5 . Gray scale and color Doppler ultrasound can also directly show a focal lumen diameter reduction. Caution should be taken when applying these thresholds at the arterial anastomosis where the normal turbulent flow leads to elevated peak systolic velocities. Ultrasound can also be used to measure flow volumes within the access (18).

Controversy surrounds the efficacy of surveillance. Studies have shown that surveillance of AVGs increases the discovery of stenoses and the number of interventions performed but does not seem to prolong their lifespan (9). In contrast, studies have shown surveillance for AVFs decreases the frequency of thrombosis and prolongs access survival (8).

Systemic anti-platelet/anticoagulation therapy

Systemic anticoagulants and anti-platelet therapy have been used to prevent access thrombosis with minimal success. One meta-analysis of anti-platelet therapy showed a decrease in early (within one month of creation) AVF thrombosis but failed to show improvement in long-term AVF patency, decrease rate of thrombosis in mature fistulas or any benefit for AVGs (19). In a randomized trial, fish oil was shown to decrease the occurrence of AVG thrombosis by 50% (20). The 2006 KDOQI guidelines do not address systemic anticoagulant use.

Pathophysiology of access thrombosis

Virchow's triad of endothelial injury, stasis and hypercoagulability can be applied to dialysis access thrombosis (21).

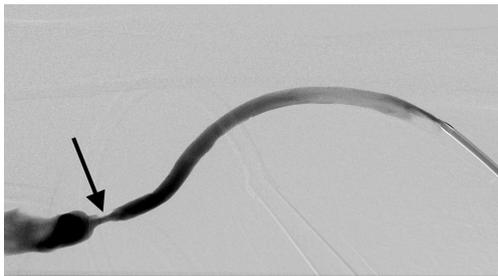


Figure 1 After surgical thrombectomy of an upper arm straight AVG, a venogram was performed which demonstrated moderate to severe focal stenosis at the graft-to-vein anastomosis (black arrow). Stenosis at this site is the most common cause of AVG thrombosis with some advocating stent graft placement for more durable access patency. AVG, arteriovenous grafts.

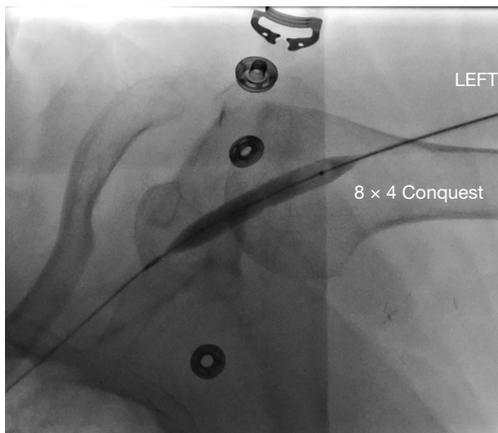


Figure 2 After percutaneous pharmacomechanical thrombolysis of a thrombosed brachiocephalic AVF, venogram showed a stenosis in the cephalic arch which was successfully dilated with a 8 mm high-pressure balloon. AVF, arteriovenous fistula.

Endothelial injury in dialysis access is multifaceted. One major component is abnormal vessel wall shear stress leading to endothelial dysfunction. Neointimal hyperplasia (discussed in detail below) leads to an altered composition of the endothelium with an abundance of extracellular matrix components on the luminal surface. Toxins from uremia also lead to endothelial dysfunction. Endothelial injury is also caused by dialysis needle punctures. Finally, in AVGs, no endothelium is present; there is an attendant 4× increase in thrombosis compared to AVFs (22,23). Endothelial injury from prior central venous catheter or transvenous pacemaker/defibrillator leads to central vein stenosis.

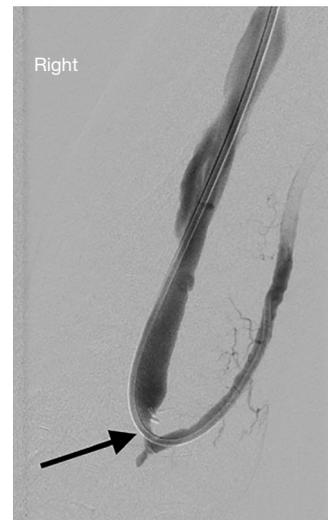


Figure 3 Fistulagram in a patient with recirculation noted at home dialysis. Stenosis was present at the juxta-anastomotic segment (black arrow) in this radiocephalic fistula. The presence of recirculation indicates that access flow rates (Q_a) are less than the set pump flow rate (Q_b), which is typically set at 300 mL/min. At this flow rate, an AVF can maintain patency but is at risk for subsequent thrombosis. AVF, arteriovenous fistula.

Stasis within a dialysis access can occur due to stenoses within the inflow, the conduit or the outflow. Poor inflow may be due to low cardiac output, systemic hypotension/hypovolemia or stenosis within the feeding artery. Within the conduit, sites of stenosis occur in relatively predictable locations. For AVGs, stenosis occurs just central to the graft-to-vein anastomosis in more than 85% of cases (24) (Figure 1). For AVFs, it depends on the type of fistula. For example, in a dysfunctional upper arm brachiocephalic fistula, the cephalic arch is stenosed in up to 77% of cases (Figure 2). In radiocephalic fistulas, the site of stenosis is the juxta-anastomotic segment in about 60% of cases (Figure 3) (25,26). These stenoses occur via a complex interplay of molecular and hemodynamic factors and have been studied most thoroughly at the graft-to-vein anastomosis. Cytokines such as hypoxia inducible factor-1 α (HIF-1 α), vascular endothelial growth factor-A (VEGF-A), matrix metalloproteinases (MMPs) and platelet-derived growth factor (PDGF) are produced by when the endothelium encounters turbulent flow, abnormal wall shear stress, vessel hypoxia and trauma. These cytokines induce the migration of fibroblasts and smooth muscles from the adventitia and media to the intima. There, they proliferate, causing

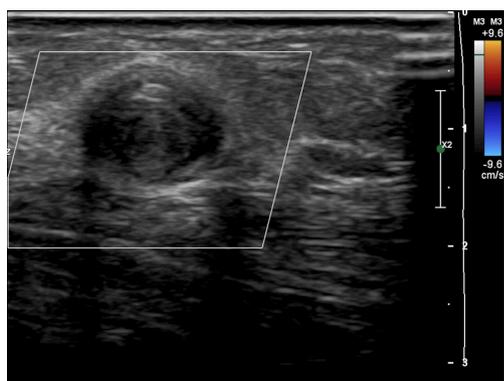


Figure 4 Pre-procedure ultrasound of a thrombosed AVG shows no flow on color Doppler ultrasound and increased echogenicity within the lumen of the AVG. AVG, arteriovenous grafts.

stenosis (27). The hormone erythropoietin (EPO), which is often given to dialysis patients, induces proliferation of endothelial progenitor cells, leading to stenosis (28). Prolonged and/or overzealous compression after needle removal may also cause stasis and thrombosis.

Until recently, hypercoagulability has been underappreciated in its role in access thrombosis. While uremia is associated with impaired platelet function, dialysis patients are in an overall prothrombotic state (29). ESRD is a chronic inflammatory state that can be objectively shown by elevated C-reactive protein (CRP) levels. Elevated CRP has been shown to be a risk factor for access thrombosis (30). Other acquired prothrombotic risk factors seen in ESRD patients include hyperhomocysteinemia, low serum albumin and elevated lipoprotein levels (31). As blood circulates through the dialysis machine, it is exposed to an artificial membrane, which activates the clotting cascade and platelets (32-34). While these effects are counterbalanced by heparinization of the access circuit, an overall pro-thrombotic state remains. Inherited thrombophilias also play a role in access thrombosis. One study reported that 55% patients with access thrombosis had at least one thrombophilic condition (35). Two of the most commonly seen inherited thrombophilias are factor V Leiden and Prothrombin G20210A (36). In patients with recurrent access thrombosis, especially without identifiable stenosis, thrombophilia should be considered as a potential cause (37).

Manifestations of access thrombosis

AVG thrombosis extends the entire length of the graft, from the arterial to the venous anastomosis. The composition

of the thrombus is predictable. At the arterial anastomosis, there is a 'white' clot, which is platelet rich. This platelet plug is resistant to tissue plasminogen activator (TPA) (38). Central to this is the 'red clot', which is fibrin rich and amenable to lysis with TPA. For AVFs the pattern of thrombosis is less predictable; it may involve a short segment or may extend to the level of the central veins.

Access thrombosis is easily diagnosed when one encounters no thrill, bruit or pulse by physical exam. By ultrasound, there will be an absence of flow on pulse-wave and color Doppler. On gray scale ultrasound, non-compressible intraluminal echogenic material is seen (*Figure 4*). In thrombosed AVFs, inflammatory thrombophlebitis, which manifests as localized redness, pain and tenderness, may occur. Inflammatory thrombophlebitis from thrombosis does not occur in AVGs; if redness and pain are encountered in a thrombosed AVG, superimposed access infection is likely (39).

Contraindications to percutaneous AV access declotting

To avoid symptomatic pulmonary emboli, declotting should not be performed in patients with poor pulmonary or cardiac reserve (40). Heart disease is prevalent in the ESRD population. The cause of cardiac dysfunction in these patients is multifactorial. First, the two most common causes of ESRD (diabetes and hypertension) are also the two of the most important risk factors for developing heart disease. Right-sided heart failure is particularly prevalent in hemodialysis patients. Pulmonary hypertension and right ventricular dysfunction is estimated to occur about 1/3rd of ESRD patients (34,41,42). Anemia and chronic volume overload leads to pulmonary volume overload. High volume AV accesses (when Q_a is >2 L/minute or $>40\%$ of the total cardiac output) play a causative role in the development of pulmonary hypertension. Pulmonary hypertension is seen at a significantly higher rate of patients dialyzed through AVFs or AVGs compared to those undergoing peritoneal dialysis or catheter based hemodialysis (43,44). Impaired right ventricular dysfunction can be assessed by evaluating for tricuspid annular plane excursion (TAPSE) (45).

Percutaneous declotting should be avoided in the setting of clotted mega-fistula as the large volume clot can cause symptomatic PE even in patients with normal heart and lung function. Percutaneous access declotting should not be performed in patients with a known right-to-left shunt as clot can go into the central arterial circulation, potentially

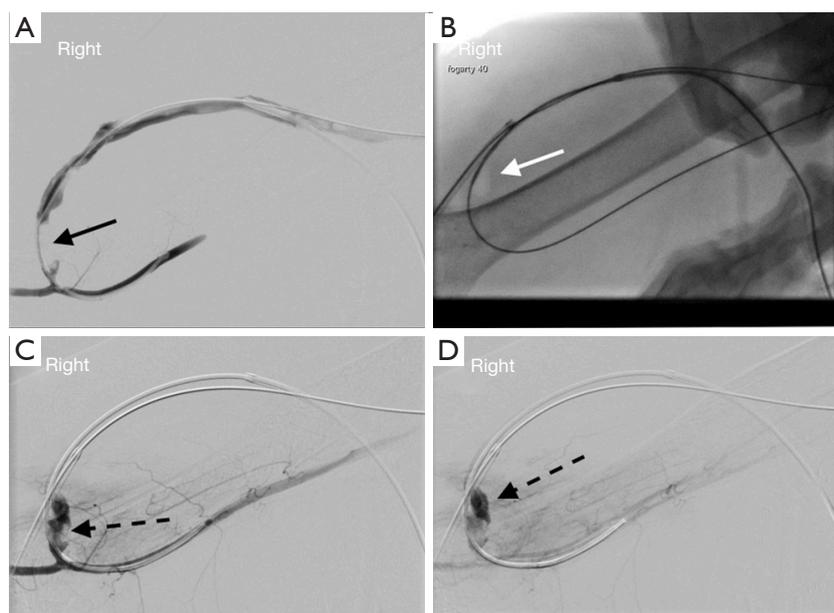


Figure 5 Intraprocedural images from a percutaneous declot of a newly placed AVG. (A) Angiogram from the feeding brachial artery shows the arterial plug (black arrow) just downstream from the arterial to graft anastomosis; (B) over a wire a 5-Fr Fogarty catheter (Edwards Lifesciences; Irvine, California, USA) was placed. The balloon was inflated with air and the plug was pulled (white arrow); (C) repeat angiogram from the feeding artery shows extravasation at the anastomosis (dotted black arrow); (D) later image from the same angiogram again shows the extravasation (dotted black arrow).

causing stroke or other complications (46,47).

In cases of poor cardio-pulmonary reserve, right to left shunt or mega-fistula, surgical thrombectomy should be considered as thrombus is externally removed from the access. This is done by first making a 2 cm near the arterial anastomosis. The platelet plug is removed using an embolectomy catheter and occasionally using forceps. The downstream clot is manually milking thrombus through this incision (48).

In patients with AV access infection, percutaneous declot can lead to the precipitation of sepsis and the development of septic pulmonary emboli. In a patient with hemodynamic instability, hyperkalemia or severe coagulopathy, declot should be performed only after the patient is stabilized. In a recently created AV access, percutaneous declotting should not be pursued for two reasons. First, the underlying problem likely needs to be fixed surgically. Second, fresh anastomotic suture lines may be disrupted (*Figure 5*). While individual practitioners vary, we suggest avoiding a percutaneous declot in an AV access which is less than 4–6 weeks old (2).

Procedural approach to percutaneous AV access declotting

Various techniques are described. Popular methods include lyse and wait (49), thromboaspiration (50), pulse spray aided pharmacomechanical thrombolysis (3), open surgical thrombectomy (51) and use of mechanical thrombectomy device such as the Arrow-Tretrotella device (Teleflex; Wayne, PA, USA) (52).

Pulse spray aided pharmacomechanical thrombolysis (Figure 6)

After one identifies the location arterial anastomosis and direction of flow within the access, the access is punctured just central to the arterial anastomosis in the direction of flow (antegrade direction) and a sheath is placed. Another sheath, at least 10 cm downstream from this antegrade sheath is placed facing the opposite direction (retrograde sheath). A wire and catheter are then advanced into the central veins and a venogram is performed. Any significant central vein stenosis is treated at this point. Then, the

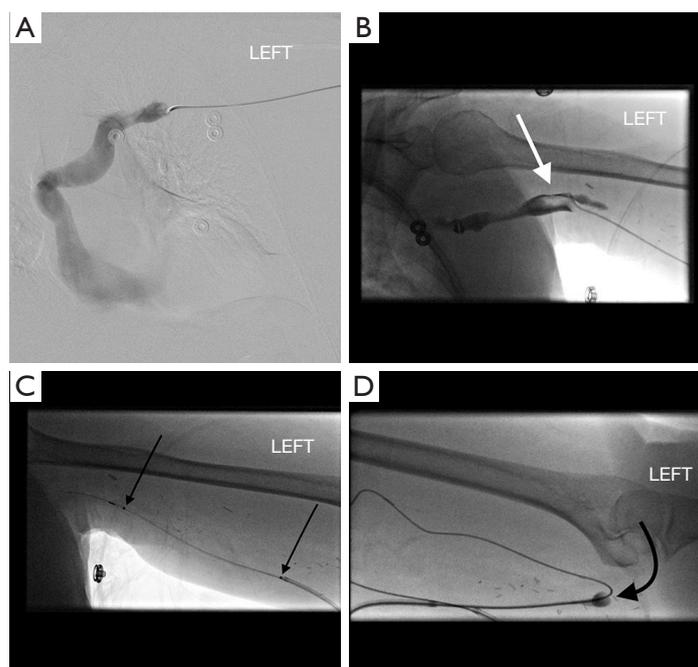


Figure 6 Intraprocedural images from a percutaneous AVF de clot. (A) After obtaining antegrade access a catheter and wire are advanced into the central veins and a central venogram is performed. If present, significant central stenosis is corrected at this time; (B) after showing patency of the central veins, a pull-back venogram was performed. This will show the most central extent of clot (white arrow); (C) over a wire, a Uni*fuse catheter (AngioDynamics; Latham, NY, USA) is placed and TPA forcefully pulse-sprayed throughout the clot in small aliquots (0.2–0.3 cc). Dark bands (skinny black arrows) demarcate length of side holes; (D) after TPA was given, balloon maceration of the clot was performed (not shown). Attention was then turned towards pulling the arterial plug. Through the retrograde sheath, a Fogarty balloon (Edwards Lifesciences; Irvine, California, USA) (curved black arrow) was advanced into the feeding artery, inflated and pulled back across the arterial anastomosis into the access.

central most extension of clot is determined by performing a pullback injection. After this is done, an infusion catheter is placed through the antegrade sheath. Starting with the most central clot, TPA is sprayed into the clot with small (0.2 cc) forceful aliquots. Overlapping TPA injection is done as the catheter is intermittently retracted to the antegrade sheath. TPA is then pulse-sprayed into the clotted segment from the central most clot to the tip of the antegrade sheath. Balloon maceration of the clot is then performed, starting at the central end of the clot. After the outflow is cleared of clot, attention is turned towards the arterial plug. As mentioned above, the platelet rich arterial plug is not amenable to TPA lysis; mechanical thrombectomy is necessary. Through the retrograde sheath, a wire and catheter are gently advanced beyond the arterial anastomosis into the feeding artery. Then, the catheter is exchanged for a deflated Fogarty® embolectomy catheter (Edwards Lifesciences Irvine, CA, USA). After this

catheter has been placed in the feeding artery, the balloon is inflated and pulled back, across the anastomosis and into the access pulling the plug into the access and centrally. The access should now be patent, which can be confirmed by physical examination, ultrasound, opening the side-arms of the sheaths or a small volume contrast injection. Once patency is confirmed, angiograms from the inflow to the right atrium should be performed and any inciting stenosis should be treated. Hemostasis can be achieved at the sheath sites with light manual pressure or with the application of purse-string sutures.

Mechanical thrombectomy with the Arrow-Trerotola device

Mechanical devices have been developed for or adapted to perform percutaneous de clot. These devices include the Arrow-Trerotola, the AngioJet™ Peripheral Thrombectomy System (Boston Scientific; Marlborough,

MA, USA) and the Argon Cleaner XT™ (Argon Medical, Plano, TX, USA). The Arrow-Trerotola device contains a rotating expandable nitinol basket that macerates thrombus as it spins at 3,000 revolutions per minute (RPMs). After placing two sheaths in the standard positions, central and pull back venograms are done and systemic heparinization is given. The compressed basket is advanced to the central most extension of clot, opened and turned on to macerate the clot while slowly pulling the device to the tip of the antegrade sheath. Once the basket reaches the tip of this sheath, the basket is collapsed and the device removed. Clot is aspirated through the sheath and the basket is cleaned. Then, the compressed basket is again advanced through this antegrade sheath and the process is repeated a few more times. A gentle angiogram can now be performed to evaluate for significant residual thrombus, which should be treated before proceeding. Once it appears that the outflow is clear of significant clot attention is turned to the inflow. The arterial plug can then be cleared using the Fogarty balloon described above or by using the basket of the Trerotola device. To use the Trerotola device, the compressed basket is advanced into the feeding artery. The basket is then opened but rotation not activated. The basket is gradually pulled back until it deforms, indicating that it is at the arterial anastomosis. At this location, the basket rotation turned on and the device slowly pulled back to the tip of the retrograde sheath. This is repeated a few times until the inflow has been cleared. A newer mechanical device by Argon medical called the CLEANER-XT™ uses a wire that rotates in a sinusoidal pattern at 4,000 RPMs. The amplitude of the sinusoidal wire matches the vessel diameter and creates a fluid vortex that macerates thrombus.

The lyse-and-wait technique

The lyse-and-wait technique utilizes the injection of TPA into the thrombosed access 30 to 120 minutes before the patient is brought to the room with a potential advantage being faster “in-room” procedure time (5). In the pre-procedure area, the access just downstream from the arterial anastomosis is prepped and draped. Antegrade puncture is done. While compressing the inflow and outflow of the access, 4 mg of TPA is injected. The catheter is secured in place and the TPA left to dwell until the procedure room is available. Subsequent initial angiogram may reveal minimal residual clot within the access outflow. The remaining steps are similar to steps described for pulse

spray aided pharmacomechanical thrombolysis above.

Complications of declotting

Significant complications of percutaneous declotting, such as symptomatic pulmonary embolism or anastomotic disruption can be avoided with proper patient selection. Meticulous procedural technique can help minimize the risk of one of the more dreaded complications of declot, embolization of the platelet plug into the artery. Manipulation at the arterial anastomosis with wires, balloon and catheters should be minimized. Additionally, the operator should avoid pressurizing the access (e.g., doing angiogram within a clotted access) as the pressure could push the arterial plug into the feeding artery. The portion of the clot that embolizes into the distal artery is the platelet rich arterial plug. Therefore, mechanical removal via back-bleeding or endovascular balloon embolectomy, thromboaspiration or surgical thrombectomy rather than TPA lysis is necessary to remove this clot (2).

Outcomes

Technically successful declotting of an acutely thrombosed AV access can be achieved in >90% of cases. The rate of success is higher for AVGs than AVFs (53). While early patency rate is high, primary patency at one year is a dismal 10–20% (54).

Conclusions

HD access thrombosis leads to missed dialysis sessions, inpatient admissions, the occasional need for temporary dialysis catheter placement and is the leading cause of permanent access loss. Access thrombosis occurs in AVGs and AVFs approximately 0.5–2.0 and 0.1 to 0.5 times per year respectively. Pre-procedure evaluation should evaluate patients for contraindications to percutaneous declotting such as known right to left shunts, access infection and poor pulmonary reserve. Many different approaches to percutaneous declotting are used. Avoiding unnecessary manipulation near the arterial anastomosis can help decrease the chances of arterial embolization.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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