Thrombolysis for the Treatment of Thrombosed Hemodialysis Access Grafts

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Maintaining the patency of hemodialysis access grafts remains problematic. It is best to recognize the failing graft prior to its thrombosis by noting an increase in recirculation, decreased flow (as measured by a Transonics device), changes in Doppler ultrasound findings, elevation of venous pressures, or swelling of the arm. If a failing graft is suspected, an angiogram should be performed to evaluate the graft. If a problem is identified it should be corrected. If it is a graft thrombosis, it can be opened using percutaneous techniques. Percutaneous declotting has been evolving since its introduction in the early 1980s. At first, a low-dose thrombolytic infusion through a single catheter was used. Crossing catheters with a higher-dose infusion was then introduced. Finally, pharmacomechanical thrombolysis, which used crossing catheters and a pulse-spray technique, became popular. Several mechanical devices have proven to be efficacious as well. In 1997, we described the "lyse-and-wait" technique. We believe "lyse and wait" to be a simpler and quicker technique, and its initial success has been similar to that for the previously described techniques. After the graft is successfully declotted, the arterial plug must be mobilized and the stenotic lesion must be addressed either by angioplasty, stent placement, surgery, or any combination of these interventions.

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There are approximately 155,000 individuals on chronic hemodialysis in the United States.[1] The number of patients undergoing hemodialysis will continue to grow as our technology improves and the survival of patients increases. Unfortunately, hemodialysis grafts are plagued with difficulties, the most common being thrombosis of the graft. It has been reported that vascular-access complications are the single largest cause of morbidity, accounting for approximately 15% of all hospitalizations in the hemodialysis population.[2] These complications add up to an annual cost to the Medicare program of between $700 and $900 million.[3]

Native arteriovenous fistulae are the preferred form of vascular access. However, more than 80% of vascular accesses in the United States are expanded polytetrafluoroethylene (ePTFE) grafts.[4] The 1-year patency rate for ePTFE hemodialysis grafts has been reported to be approximately 65%.[5,6] An estimated 60% of individuals with an ePTFE graft will need to undergo at least 1 revision per year.[7] The most common cause of graft failure is thrombosis secondary to progressive luminal narrowing (stenosis).[8–14] For years, surgical thrombectomy with or without graft revision or complete graft replacement has been the standard of treatment for a failed graft. Surgical thrombectomy alone is usually not curative, because the etiology of the graft thrombosis is not addressed. In the operating room, the surgeon must perform an intraoperative angiogram or a blind exploration after declotting the graft to properly visualize and treat the cause of thrombosis. However, by choosing to declot the graft percutaneously, one can fluoroscopically evaluate the arterial anastomosis, graft, venous anastomosis, and more central veins in search of an anatomic cause for the failure.

The challenge of determining the most effective treatment for thrombosed grafts is paramount in the minds of the nephrologists, the access surgeons, and the interventional radiologists. Therefore, a team approach is warranted that incorporates graft screening by the nephrologist to prevent thrombosis; percutaneous declotting and angioplasty by the interventional radiologist once the graft clots; and surgical thrombectomy/graft revision by the access surgeon if percutaneous repair has failed or is deemed inappropriate. This review discusses how best to manage the failing and failed hemodialysis grafts.

Graft Surveillance

The goal of a screening program is to identify a failing graft, thus allowing early intervention and prevention of the failure. An ideal screening examination must identify significant lesions and be inexpensive, noninvasive, and not operator-dependent. There is no single modality that meets these requirements. All of the modalities that will be discussed generally identify flow-reducing stenoses. Grafts that fail without a stenosis-related etiology will go undetected. The failure of a graft without an anatomic cause may be due to hypotension, hypercoagulopathy, or hemoconcentration of the blood (dehydration).

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A physical examination is a screening modality that is low in cost and noninvasive. The physical examination can be divided into 2 parts: 1) examination of the extremity, and 2) examination of the graft. With respect to the extremity, a swollen extremity usually reflects the presence of a central venous stenosis or occlusion. The edema in the extremity results from high venous pressure. Multiple collateral veins may form to circumvent the central lesion.[15] A physical examination also includes inspection of the graft for a pulse and a thrill. A nonfailing graft should have a thrill within the graft with some mixed pulsations near the arterial anastomosis. Therefore, as an outflow stenosis occurs, the thrill within the graft is lost, and the graft becomes pulsatile up to the point of the lesion. One study has shown that the presence of a thrill throughout the graft rules out the low graft-flow associated with impending failure of the graft.[16] The absence of a thrill in this study was nonspecific.

A Doppler ultrasound examination can be effective in measuring flow-velocities and identifying stenoses by focal accelerations of blood.[17,18] It can effectively predict which grafts are at an increased risk for failure. However, Doppler ultrasound examinations are prohibitively expensive, operator-dependent, and lack repeatability to be used as a routine screening modality. If the results of other screening modalities are equivocal, then prior to angiography, a Doppler ultrasound may be obtained to assess the graft.

Percent recirculation of dialyzed blood is another method utilized to evaluate dialysis grafts. This represents the amount of dialyzed blood being withdrawn from the access for repeat dialysis without having gone through the systemic circulation. As the graft blood-flow decreases secondary to an outflow stenosis, the percentage of recirculated blood increases. One study demonstrated that 82% of patients with stenoses had a significant amount of recirculation.[19] Unfortunately, it is now recognized that recirculation appears quite late in the natural history of a failing graft.[20] Therefore, percent recirculation is not an ideal screening method because many failing grafts would not be identified.

Measuring intra-graft pressure is another screening modality used to identify the failing graft. Intra-graft pressure measurements can be

obtained during dialysis with a pressure transducer attached to the outflow line via a stopcock, or a static pressure measurement can be obtained with the dialysis machine turned off. Systolic intra-graft pressure is compared to the systemic systolic blood pressure measured from a blood pressure cuff, yielding a normalized ratio (static intra-graft pressure/systolic blood pressure). This ratio can be obtained during repeat dialysis and usually remains constant in the individual patient despite fluctuations in systemic blood pressure. It has been demonstrated that a normalized ratio greater than 0.4 has the highest sensitivity (91%) and specificity (86%) for identifying venous outflow lesions greater than 50%.[20] It has also been demonstrated that patients with stenoses identified by increased venous dialysis pressures (> 150 mm Hg at a flow rate of 200–225 mL/min) had an approximately 10 times higher risk of thrombosis than patients with normal pressures.[12]

It is now possible to directly measure flow by using a Transonic HD01 system (Transonic Systems, Ithaca, NY). Actual flow is measured during dialysis and can be followed on a monthly basis. When the flow falls below 600 cc/min the graft should be evaluated with venography. In addition, any significant decrease in flow (ie, a decrease by more than 25% over a 4-month period) should be evaluated.

Graft Failure

Unfortunately, despite the best intentions of the nephrologist, access surgeon, and interventional radiologist, hemodialysis grafts do thrombose. Once the failure of the graft is recognized, a decision must be made as to how to treat the patient most effectively.

Traditionally, thromboses of hemodialysis grafts have been treated by surgical thrombectomy with or without revision. Surgical salvage of the graft usually entails accessing the graft via a short incision over the venous limb of the graft or by opening the previous incision used to place the shunt. Next, thrombectomy is performed using balloon thrombectomy catheters (eg, Fogarty catheter, Edwards, Irvine, CA). Depending on the operating room facilities, either an angiogram is performed or the venous anastomosis is directly inspected to evaluate the graft for any evidence of stenosis. If a lesion is identified, the graft is revised either by using a jump graft to a more proximal vein using PTFE or by a patch angioplasty across the stenotic lesion.

Several studies have compared the efficacy of percutaneous and surgical treatment.[21,22] The studies have shown comparable patency rates with angioplasty and surgery, with no statistically significant difference between the two treatments. Primary patency rates at 1 month for angioplasty and surgery are similar, ranging from 72%–77% and 64%–86%, respectively.

Another study examined the results of graft-salvage by surgical thrombectomy alone versus surgical thrombectomy with graft revision. The retrospective study of 116 surgical thrombectomies or revisions found discouraging results showing patency rates of 59% at 30 days and 25% at 120 days for revised grafts versus even worse results, 30% at 30 days and 10% at 120 days for grafts treated only with surgical thrombectomy.[23] The investigators concluded that thrombosed grafts should be abandoned in favor of a new access site. However, each graft revision, extension, or new graft placement is performed at the expense of valuable vein. Percutaneous declotting with an evaluation and treatment of the stenotic lesion may spare vein and prolong the use of an extremity for hemodialysis.

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Pharmacologic Thrombolysis

Pharmacologic thrombolysis of thrombosed hemodialysis grafts was first attempted in the mid-1980s. Initially, streptokinase was used; streptokinase was infused into the afferent limb of the thrombosed graft. Early reports demonstrated streptokinase's effectiveness at dissolving a clot and restoring blood flow in the graft.[24] Unfortunately, the majority of patients suffered local bleeding complications from previous dialysis puncture sites, and other patients suffered allergic reactions. Furthermore, with repeated treatments, the patients developed resistance to streptokinase. These difficulties led to the abandonment of streptokinase as a thrombolytic agent for clotted grafts.

Urokinase (UK) was then studied as a hemodialysis graft-declotting agent. It was first used as a drip infusion. The initial success (patency at 24–48 hours with successful dialysis) ranged between 49% and 79%, and the length of infusion times varied from 2–20 hours.[25–28] UK drip infusions were, however, plagued with the same local hemorrhagic complications seen in the streptokinase trials; up to 50% of the patients experienced bleeding difficulties.

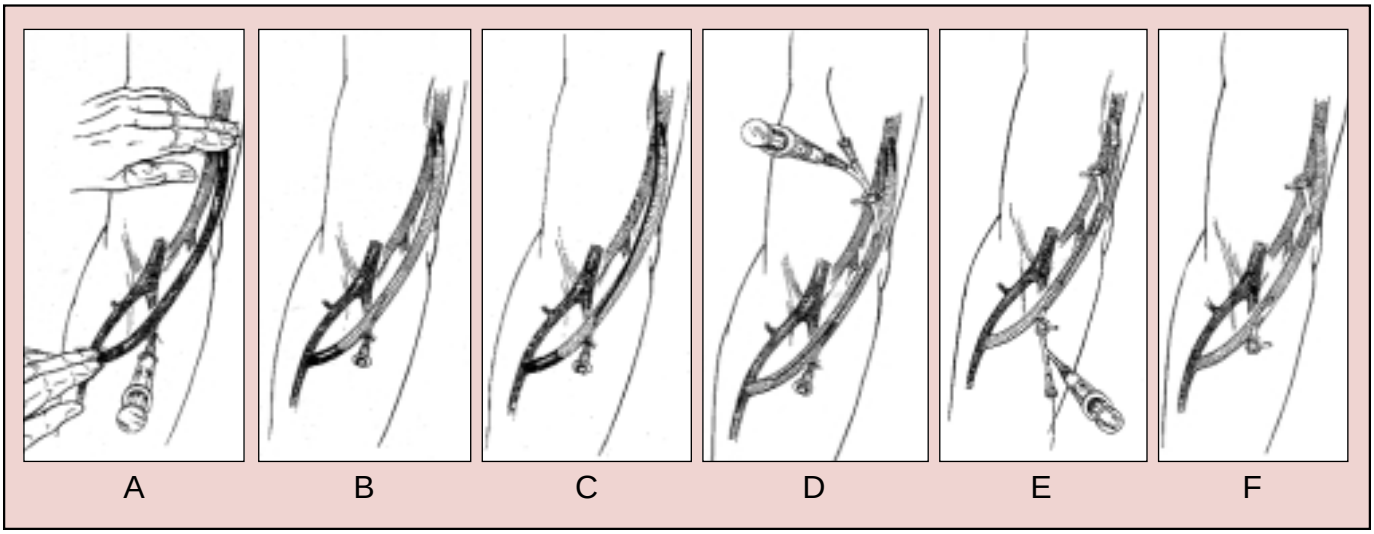

Figure 1. *Description of the lyse-and-wait technique:* **(A)** *an Angiocath is introduced into the clotted graft, and a lytic agent is introduced while compressing the inflow and outflow;* **(B)** *an angiogram, after waiting 30–45 minutes, demonstrates minimal or no residual clot;* **(C)** *a venous lesion is crossed and the Angiocath is replaced by a 4-F catheter;* **(D)** *Fogarty manipulation of an arterial (platelet-rich) plug;* **(E)** *angioplasty of venous lesion (steps* **[D]** *and* **[E]** *may be reversed) and any mid-graft or central lesions;* **(F)** *the entire graft and central circulation is studied, and pressures or flow are measured to ensure a good result.*

Pharmacomechanical Thrombolysis

"Lacing/Maceration"

In an attempt to shorten infusion times, reduce UK dosages, and decrease hemorrhagic complications, research began adding a mechanical component to the already-developed pharmacologic thrombolytic techniques. One group developed a novel technique termed "lacing/maceration."[29] Two 5-F dilators were placed into the midportion of the graft in a criss-cross fashion. After the initial graft was evaluated and the dilators were exchanged for two hook-shaped catheters, highly concentrated UK (25,000 IU/mL) was injected through the catheters, which were rotated and withdrawn through the thrombosed graft. After the catheters were repositioned at the midportion and the arterial end of the graft, an infusion of UK (4000 IU/mL) was then started at 2000 IU/min per catheter until the graft was clot-free. Any identified stenoses were then subject to angioplasty. The major advantages of this declotting technique were a decreased infusion time, with an average infusion time of 86 minutes, and a 90% initial success rate with no reported hemorrhagic complications.

"Pulse-Spray" Technique

The same group of investigators modified the lacing/maceration technique and eliminated the need for the supplemental UK infusion after the lacing. This so-called "pulse-spray" technique used two crossed, tapered catheters with multiple side holes and forcefully injected highly concentrated UK into the clot.[30] When the graft appeared to be relatively clot-free, an angiogram was performed with a subsequent angioplasty to address any stenotic lesions. This pulse-spray method reduced the mean infusion time from 86 minutes, shown in the previously described lacing/maceration technique,[29] to 49 minutes. In this series, initial success was achieved in 97.9% of the cases. These investigators reported a discouraging 1-year primary patency rate of 26%.[31] After repeated procedures, however, the secondary patency rate increased to 51%. Again, no hemorrhagic complications were reported.

The pulse-spray technique was later modified by including the early fragmentation of a residual clot with a balloon catheter, intrathrombic injection of heparin, mechanical treatment of a lysis-resistant plug at the arterial anastomosis, and the routine administration of aspirin. In 1995, the original and modified techniques were retrospectively compared.[32] Using the modified technique, the mean thrombolytic-

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agent infusion time was reduced from 44 to 23 minutes and the initial success rate increased from 86% to 96%, with 92% remaining patent for at least 24 hours. The complication rates between the original and modified techniques were not significantly different. Even though the modifications did not significantly improve the initial success rate, the mean infusion time decreased dramatically. Follow-up studies using the modified pulse-spray technique reported the 30- and 90-day primary patencies to be in ranges of 70% and 50%, respectively.[33–36] One study demonstrated a 30-day secondary patency rate of 92%.[33]

The "Lyse-and-Wait" Technique

As first described by our group, the "lyse-and-wait" technique (Figure 1) is a simplified lytic method that can be used to treat thrombosed hemodialysis grafts.[37] This technique eliminates the need for any mechanical devices[38–45] or pulse-spray catheters. No time is spent in the angiography suite declotting the graft, because there is usually only a minimal or no residual clot in the graft, at the start of the fluoroscopic portion of the procedure. The lyse-and-wait technique eliminates the need to use pulse-spray thrombolysis or mechanical declotting, thus simplifying and shortening the procedure. As no time is spent on declotting the graft, more attention can be focused on achieving an adequate angioplasty.[37]

Before the patient is brought into the angiography suite, a 22-gauge angiocatheter is introduced into the graft close to the arterial anastomosis, pointing toward the venous anastomosis. Confirmation of the intra-graft placement of the catheter is obtained by visualizing blood or a clot exiting the catheter. If no blood or clot is initially seen, the graft is compressed and milked to force a clot into the catheter. If there is still no return, a 0.018-inch short guidewire can be inserted through the angiocatheter. If the guidewire travels smoothly without any resistance or pain, this is additional confirmation of the intragraft position of the angiocatheter. When the wire is removed, there will often be a return of blood or a clot, as the guidewire causes disruption of the organized clot at the tip of the angiocatheter. Once the intragraft angiocatheter position is confirmed by the above methods, the graft is compressed at the arterial and venous anastomoses while a UK (Abbokinase, Abbott Laboratories, Abbott Park, IL)-heparin mixture (250,000 IU of UK [5 mL] and 5000 U of heparin [1 mL]) is infused slowly over 1–2 minutes. Alternatively, we used 2–5 mg of recombinant tissue plasminogen activator (rt-PA) (when UK became unavailable), and 5000 U of heparin was given systemically. Others have also demonstrated the use of UK at lower doses.

After approximately 30–45 minutes, the patient is brought into the angiography suite, and the arm is prepared and draped in the usual fashion. An angiogram is then obtained that typically shows minimal-to-no clot within the graft. We first exchange the 22-gauge angiocatheter to a 4-F dilator with the use of a 0.018-inch guidewire. We then cross the venous anastomosis using a 4-F directional catheter. Our attention is then focused on mobilizing the arterial plug that is usually present close to the arterial anastomosis. This is accomplished by introducing a short 5-F or 6-F sheath into the graft via a puncture close to the venous anastomosis, pointing toward the arterial anastomosis. The arterial plug is mobilized toward the venous side of the graft using a 4-F or 5-F "Thru-Lumen" Fogarty balloon (Baxter Healthcare, Santa Ana, CA). Next, using a 6-, 7-, or 8-mm high-pressure balloon, the venous lesion is dilated. The access from the arterial anastomosis to the right atrium is then evaluated angiographically. After the graft is free of clot, the venous lesion has been dilated, there is a thrill in the graft, and the intragraft pressure is approximately 40% of the systemic pressure, the graft is ready for dialysis.

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Since we originally described the lyse-and-wait technique in the *Journal of Vascular and Interventional Radiology*,[37] we have performed a prospective, multicenter, randomized trial comparing lyse and wait with the use of UK to the most common lytic technique, the modified pulse-spray technique. Of 87 patients who were randomized, 43 were treated with lyse and wait and 44 with pulse-spray lysis. The technical success was 98% and 100%, respectively. The procedure time, defined as the length of time from when local anesthesia was given until the last venogram, was 45.8 minutes for lyse and wait and 65.5 minutes for pulse-spray ($P < 0.001$). The 1- and 3-month patency was similar in both groups—76.9% and 58.1% for pulse spray and 79.5% and 55.3% for lyse and wait, respectively.[46]

Vogel and colleagues[47] published

results of a randomized study comparing lyse and wait using rt-PA with the Percutaneous Thrombolytic Device (PTD) (Arrow-Trerotola). They also compared these results with findings from a group of 20 patients that they had entered into the UK lyse-and-wait trial versus pulse-spray study discussed above.[46] The initial success was 95% in all three groups. The lysis time was shortest for patients receiving rt-PA (10 min vs 19 min for UK and 19 min for PTD); however, the room time was shortest for the group receiving UK (34 min vs 39 min for rt-PA and 45 min for PTD). In addition, the hemostasis time was significantly longer for the rt-PA group, and there were more bleeds in the rt-PA group. Purse-string sutures were not used in any of these cases; manual compression was used to achieve hemostasis. It is likely that the increased compression time and bleeding complications were related to the lytic used. However, in our experience with the use of purse strings we have not had any significant bleeds. We are currently removing all catheters and sheaths immediately after the procedure with the use of a purse-string suture.

Although many devices have been introduced to declot grafts more rapidly, no device eliminates the declotting altogether.

Discussion

Percutaneous arteriovenous graft declotting has become the primary means of treating thrombosed grafts in many institutions. Although many interventional radiologists declot grafts without concern for pulmonary emboli and have described excellent initial success,[32,36,49–52] some have been reluctant to treat clotted grafts in this fashion because of the theoretical risk of pulmonary emboli and the technical difficulty they may have encountered in clearing the graft and obtaining adequate results. In addition, the operator's hands may have been exposed to excessive radiation during the many catheter maneuvers that are required to successfully declot grafts with the use of pulse-spray and mechanical techniques. The modifications to pulse-spray pharmacomechanical thrombolysis that we describe address these issues.

Standard hemodialysis graft declotting can be divided into five separate and distinct steps. The first step is accessing the graft in two locations with crossing catheters, one directed toward the arterial anastomosis and the other toward the venous anastomosis. The venous anastomosis and the central veins can be evaluated at this point. If the venous lesion is believed to be long and not amenable to percutaneous treatment, some angiographers may stop at this point and recommend a surgical thrombectomy and revision. If the venous lesion is deemed repairable, the next step is declotting the graft. This can be performed with a thrombolytic technique or by using a U.S. Food and Drug Administration–approved mechanical thrombectomy device. Mobilizing or crushing the arterial plug that usually forms at the arterial anastomosis and treating the stenotic vein that caused the thrombosis (not necessarily in that order) are the next steps. The final step is removing the catheters or sheaths. Although for a while we had been leaving the sheaths in for dialysis, currently we are removing the sheaths immediately after the procedure using a purse string suture.[48]

Although many devices have been introduced to declot grafts more rapidly, no device eliminates the declotting altogether.[39–45,53] By introducing the lytic agent before bringing the patient into the angiography suite, the declotting portion of the procedure requires essentially no operator and no room time. It has been stated that patency is probably not dependent on the technique used to declot the graft. Rather it is probably most dependent on the success of the angioplasty performed on the venous lesion. Room time is spent on the more critical portion of the procedure, evaluating and treating the venous lesion and evaluating and treating the arterial plug that may exist at the arterial anastomosis. With the graft relatively free of clot, a more accurate picture of the venous lesion can be obtained. A vein that appears diffusely narrowed while the graft is occluded may be relatively normal in size with a focal lesion when the graft is pressurized. Therefore, we maintain that the graft should be declotted even if the venous lesion appears long. If the graft fails soon after percutaneous declotting, surgical revision should be considered. Because the graft is

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free of significant clot at the start of the procedure, the risk of pulmonary emboli is probably lessened. By deleting the pulse-spray or mechanical declotting portion of the procedure and simplifying the management of the arterial plug, it is likely that exposure of the operator's hands to radiation will be significantly reduced, and the procedure time will be shortened.

The management of the venous lesion is not altered by this technique. Often, several prolonged dilations are necessary to achieve an adequate result. The use of stents or atherectomy devices to treat the venous stenosis remains controversial.[24] In addition, the arterial plug is not always easily mobilized. Several passes may be necessary to clear the plug. Thru-Lumen Fogarty catheters are now available and are useful in cases where crossing the arterial anastomosis with a balloon thromboembolectomy catheter proves difficult. The overall procedure time is composed of the time for all these maneuvers.

The lyse-and-wait technique addresses many of the issues that have limited the acceptability of percutaneous hemodialysis graft declotting among interventional radiologists. It is a relatively simple procedure that can be performed by any interventional radiologist competent in the performance of a venous angioplasty.

Conclusion

In conclusion, although the results of percutaneous and surgical declotting of occluded dialysis grafts are similar, percutaneous declotting has many advantages: it is less invasive, spares the sacrifice of additional vein, is easily repeatable, and most importantly, allows for the evaluation of the entire circulation from the arterial anastomosis to the right atrium.

Percutaneous declotting can be performed with mechanical devices or with thrombolysis. Thrombolysis has evolved over the past several years. The most popular techniques used today are either the pulse-spray or the lyse-and-wait techniques. The lyse-and-wait technique is effective, simpler, and probably quicker and more cost-effective than any of the previously reported techniques. ■

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Main Points

- More than 80% of vascular accesses in the United States are expanded polytetrafluoroethylene (ePTFE) grafts. The 1-year patency rate for ePTFE hemodialysis grafts has been reported to be approximately 65%, and an estimated 60% of individuals with an ePTFE graft will need to undergo at least 1 revision per year.
- The most common problem with hemodialysis access grafts is thrombosis of the graft secondary to progressive luminal narrowing (stenosis).
- Physicians should recognize the failing graft before its thrombosis by noting an increase in recirculation, decreased flow, changes in Doppler ultrasound findings, elevation of venous pressures, or swelling of the arm. If a failing graft is suspected, an angiogram should be performed to evaluate the graft.
- For years, surgical thrombectomy with or without graft revision or complete graft replacement has been the standard of treatment for a failed graft.
- Percutaneous declotting has evolved as a technique since its introduction in the early 1980s, and it can be performed with mechanical devices or with thrombolysis. Pharmacomechanical thrombolysis, which uses crossing catheters and a pulse-spray technique, has become an increasingly popular treatment.
- Although the results of percutaneous and surgical declotting of occluded dialysis grafts are similar, percutaneous declotting has many advantages: it is less invasive, spares the sacrifice of additional vein, is easily repeatable, and most importantly, allows for the evaluation of the entire circulation from the arterial anastomosis to the right atrium.
- The lyse-and-wait technique addresses many of the issues that have limited the acceptability of percutaneous hemodialysis graft declotting among interventional radiologists.
- The most popular percutaneous thrombolytic techniques used today are either the pulse-spray or the lyse-and-wait techniques. The lyse-and-wait technique is effective, simpler, and probably quicker and more cost-effective than any of the previously reported techniques.

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